February 22, 2016

Division of Dockets Management
Food and Drug Administration
5630 Fishers Lane
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Rockville, MD 20852

CITIZEN PETITION

The undersigned submit this petition pursuant to Title 21, Chapter 9, Subchapter V, Part A of the Federal Food, Drug, and Cosmetic Act and 21 C.F.R. § 10.30 to request that the Commissioner of the U.S. Food and Drug Administration (FDA) place a black box warning on pharmaceuticals in the opioid and benzodiazepine classes warning patients of the potential serious risks with concomitant use of both classes of medications.

ACTION REQUESTED

The Petitioner requests the FDA to:

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

   a. Labeling for all Opioid Class Medications should 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 should 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.

2. Require medication guides for both classes of medications that specifically warn patients of the potential dangers of combined use of opioids and benzodiazepines.
STATEMENT OF GROUNDS

I. OVERVIEW

Concurrent misuse of benzodiazepines and opioids is contributing to the epidemic of fatal overdose in the United States. Biological data indicate that these two drug classes have synergistic effects in producing sedation and respiratory depression. Epidemiological data show polysubstance overdose fatalities involving both opioids and benzodiazepines are common and increasing.

FDA guidance indicates that a black box warning is appropriate in several circumstances, including when:¹

- “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 severity by appropriate use of the drug (e.g., patient selection, careful monitoring, avoiding certain concomitant therapy, addition of another drug or managing patients in a specific manner, avoiding use in a specific clinical situation)”

Both of these conditions are met in this case. Clinicians should consider the serious adverse reaction of fatal overdose when assessing the risks and benefits of co-prescribing benzodiazepines and opioids. Moreover, clinicians can prevent fatal overdose by reducing rates of co-prescribing these classes of medications.

The labels and medication guides of only a few drugs in these two classes contain specific information on the dangers of concurrent use; none contain black box warnings. Accordingly, we are petitioning the FDA to add black box warnings for all medications in the opioid and benzodiazepine classes that appropriately warn prescribers and patients about a

reduced margin of safety and increased risk of fatal overdose when these classes of medication are used together.

II. BIOLOGY

Benzodiazepines and opioids operate on different receptors and have been long-understood to have synergistic effects on sedation and respiratory depression, such that concurrent use lowers the margin of safety.

**Benzodiazepines.** The primary allosteric mechanism of action for benzodiazepines is through binding to gamma-aminobutyric acid (GABA) receptors. This increases the activity of GABA, the principal, endogenous, inhibitory neurotransmitter in the central nervous system.\(^2\) Benzodiazepines are known to decrease oropharyngeal muscle tone and blunt the arousal response to hypoxia and hypercapnia during sleep and thus increase risk of sleep apnea, even among healthy individuals.\(^3,4\) In addition to their other properties, such as anti-seizure activity, benzodiazepines are known to enhance the sedating effects of other medications and substances, including: full-agonist opioids, partial agonist opioids such as buprenorphine, alcohol, barbiturates, and sedating antihistamines.\(^5\)

**Opioids.** Opioids, in addition to acting as potent analgesics, cause sedation up to and including complete loss of consciousness and respiratory arrest. Opioids function primarily through stimulation of the Mu (\(\mu\)), Kappa (\(\kappa\)), and Delta (\(\delta\)) receptors that are normally activated in response to noxious stimuli by endogenous molecules (endorphins, enkephalins, and dynorphins). In addition to analgesia, stimulation of Mu receptors in the brainstem and medial thalamus causes respiratory depression and sedation, particularly in non-tolerant individuals. Kappa receptors (found in limbic and other diencephalic areas of the brain, the brainstem, and spinal cord) mediate spinal analgesia, sedation, dyspnea, and respiratory depression.\(^6\)


Laboratory and Human Subject Studies on Concurrent Use. Receptors for both opioids and benzodiazepines are highly concentrated in the respiratory centers of the medulla. Multiple laboratory studies in animals and humans have indicated that co-administration of these drugs decreases the margin of safety with respect to respiratory depression.

For example, a study in rats demonstrated that while high doses of an opioid (buprenorphine) and a benzodiazepine (midazolam) alone both resulted in mild, but significant increases in PaCO2, the combined administration of these two drugs resulted in rapid, substantial and prolonged respiratory depression and hypoxia.

Studies of human subjects have found synergistic effects in combining opioids with benzodiazepines:

- An experimental study on the effects of administering sedative doses of fentanyl, midazolam, or fentanyl plus midazolam, in 12 healthy adult males found fentanyl alone produced hypoxemia in 50% of subjects and apnea in none; the combination produced hypoxemia in 11 of 12 participants and apnea in half of the subjects.

- An experimental study on the effects of co-administering high dose diazepam (40mg) with high dose methadone among patients maintained on regular opioid therapy (buprenorphine or methadone) found decreased SpO2 levels in the methadone group at 150% of normal dose, demonstrating a synergistic effect on respiratory depression. (This effect was not seen with buprenorphine in this study.)

- Utah researchers conducted diagnostic polysomnographies on 140 patients with chronic pain who had been maintained on daily opioid therapy for at least 6 months, with a stable dose for at least 4 weeks. The patients were taking a variety of medication regimens, including benzodiazepines, muscle relaxants, and others. Of assessed combinations, the only medication usage pattern that had a statistically significant impact on the central apnea index was the combined used of methadone and

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9 Bailey, PL, Pace, NL, Ashburn, MA, Moll, JWB, East, KA, Stanley, TH. Frequent Hypoxemia and Apnea after Sedation with Midazolam and Fentanyl. *Anesthesiology*. 1990; 73:826-830.

benzodiazepines. The authors reported that “...benzodiazepines appeared to have an additive effect to the prevalence of methadone-related central sleep apnea.”

Of note, the danger of combining benzodiazepines and opioids has not always been observed at therapeutic doses of both medication classes. For example, in one study, therapeutic doses of diazepam in 16 patients on stable methadone or buprenorphine regimens caused sedation and subtle performance deficits in reaction time, but not physiologic changes in pulse, blood pressure, respiratory rate, or SpO2.

Investigators have proposed potential mechanisms to explain the synergistic impact of opioids and benzodiazepines. It is generally thought that buprenorphine, a partial opioid agonist that is normally rarely associated with overdose death due to its natural ceiling effect for respiratory depression, loses this ceiling effect when taken in combination with benzodiazepines, resulting in risk of respiratory depression and death. Other potential mechanisms include: (1) benzodiazepines may alter the pharmacokinetics of opioids through noncompetitive inhibition of opioid metabolism, (2) the analgesic, hyperphagic/hyperdipsic, anxiolytic, and rewarding effects of benzodiazepines may be partially mediated via opioidergic mechanisms, and (3) benzodiazepines may amplify the Mu agonist effects of opioids.

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III. EPIDEMIOLOGY

Complementing the biological evidence, data from multiple sources indicate that concurrent use and misuse of benzodiazepines and opioids is associated with addiction and overdose.

*Data from Treatment Admissions.* Studies of patient perception have shown that benzodiazepines potentiate the intensity and duration of the analgesic, euphoric, and sedative effects of opioids in a dose-response pattern, indicating potential for misuse and addiction.\(^{16}\) Indeed, substance use disorders involving both opioids and benzodiazepines appear to be sharply increasing. According to the Substance Abuse Mental Health Services Administration, treatment admissions due to co-occurring addiction to benzodiazepines and opioids increased 569.7% from 2000 to 2010, while admissions due to all other substance use disorders decreased by 9.6% in the same time period.\(^{17}\) (see Figure). During the month prior to treatment admission, of patients admitted for co-use of opioids and benzodiazepines, 57.1% and 45.5% reported daily use of opioids and benzodiazepines, respectively.\(^{18}\)

*Data from Death Certificates and Autopsies.* The combination of benzodiazepines and opioids is becoming increasingly common in overdose deaths. Moreover, there is epidemiological evidence of a synergistic effect of the combination on the risk of death.

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\(^{16}\) Ibid.


\(^{18}\) Ibid.
A recently published six-year case-cohort study of U.S. veterans nation-wide analyzed the relationship between history of benzodiazepine prescription, dose, type, and schedule and the associated risk of death from a drug overdose among patients who received treatment with opioid analgesics from the Veterans Health Administration. Study groups included veterans who died of a drug overdose and received opioids (n=2400) and a random sample of veterans who received opioid analgesics and services (n=420,386) from 2004 to 2009. During this study period, “...about half of the deaths from drug overdose (n=1185) occurred when veterans were concurrently prescribed benzodiazepines and opioids.”

Significantly, the risk of death from drug overdose increased in a synergistic, dose-response fashion as daily benzodiazepine dose increased, as shown in the Figure. This risk was independent of dosing schedule.

The authors also found risk of death from overdose increased with history of benzodiazepine prescription, with the greatest risk associated with a current prescription.19

Epidemiological data show a high rate of involvement of benzodiazepines in opioid-related overdose deaths. For example:

- According to data from the National Vital Statistics System, 17% of the 13,800 opioid analgesic related deaths in 2006 involved concurrent use of benzodiazepines.20 This rate of benzodiazepine involvement increased to 30% by 2010.21

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• In 2012 in New York State, of 883 opioid analgesic-related deaths, 308 (34%) involved benzodiazepines.\textsuperscript{22}

• According to data from the Rhode Island Department of Health, benzodiazepines were involved in 33% of prescription opioid fatalities from 2014 to 2015.\textsuperscript{23}

• Maryland found benzodiazepines to be associated with 17.4% of prescription opioid deaths in 2012, 15.8% in 2013 and 18.5% in 2014.\textsuperscript{24,25}

These data complement older data showing high rates of concurrent use of benzodiazepines in opioid overdose:

• A study reviewing death certificate data from 1999 to 2009 using the CDC Wide-Ranging Online Data for Epidemiologic Research database found benzodiazepines with opioids to be the most common polysubstance overdose fatality among 15 to 64 year olds.\textsuperscript{26}

• A review of 493 methadone-associated deaths in New York City from 2003 found 32% involved benzodiazepines,\textsuperscript{27} a review of 139 methadone-associated deaths in Palm Beach from 1998 to 2002 found 33% involved benzodiazepines,\textsuperscript{28} and a review of 84


methadone-associated deaths in Australia from 1993 to 1999 found 74% involved benzodiazepines.  

- In a comprehensive assessment of 117 fatalities from 1996 to 2000 involving high-dose buprenorphine in France, benzodiazepines were involved in at least 91 (78%).
- A 1999 study of 82 opioid-related deaths in Ireland found benzodiazepines identified in 52 (61%) of the deaths.

While most studies and attention have focused on the involvement of benzodiazepines in opioid-related deaths, the converse is also true: There is an extraordinarily high rate of opioid involvement in benzodiazepine associated deaths. For example, in Maryland, 74.0% of benzodiazepine associated deaths in 2012, 72.5% in 2013, and 59.2% in 2014 involved prescription opioids.

IV. CLINICAL EDUCATION

Prescribers need to consider the serious adverse reaction of fatal overdose when assessing the risks and benefits of co-prescribing benzodiazepines and opioids. However, existing educational measures have not been sufficient for this purpose. As a result, a black box warning would provide significant benefit.

Prescribing Trends. The CDC’s 2014 Vital Signs brief reported that prescribers wrote 82.5 opioid prescriptions and 37.6 benzodiazepine prescriptions per 100 persons in the United States in 2012. Evidence indicates rates of co-prescription are rising. According to a study based on a database of 3.1 billion primary care visits, from 2002 to 2009, concurrent prescription of benzodiazepines with opioids increased by 12.0% per year, and benzodiazepine

[33] Maryland Department of Health and Mental Hygiene 2015, op. cit.
prescriptions increased by 12.5% per year. During this time, 12.6% of all primary care visits involved benzodiazepine or opioid prescriptions.\textsuperscript{35}

Rhode Island has also seen increasing numbers of patients receiving both benzodiazepines and opioids, as shown in the figure below.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure.png}
\caption{Average number of people dispensed both a benzodiazepine and an opioid medication within 30 days in Rhode Island}
\end{figure}

Data from the Rhode Island Department of Health illustrate the frequency of co-prescription. Among all patients dispensed an opioid in the state in 2015, 27% also were dispensed a benzodiazepine at least once within 30 days of receiving an opioid. Of those dispensed a benzodiazepine, 59% were also dispensed an opioid at least once within 30 days of receiving a benzodiazepine.\textsuperscript{36}

Based on such data, Rhode Island has set a priority of reducing co-prescription of benzodiazepines with opioids as a key component of their state’s strategy to reduce prescription drug-related deaths.\textsuperscript{37}

A common clinical scenario for co-prescription of opioids and benzodiazepines is the patient with chronic pain. Patients who receive opioids for chronic pain are often also prescribed benzodiazepines for associated symptoms including muscle spasms, anxiety and sleep disorder despite little evidence for therapeutic benefit in this clinical situation. In a


\textsuperscript{36} Rhode Island Governor’s Overdose Prevention and Intervention Task Force, \textit{op. cit.}

\textsuperscript{37} Rhode Island Governor’s Overdose Prevention and Intervention Task Force, \textit{op. cit.}
A national sample of chronic non cancer pain patients prescribed opioids, approximately one-third were current users of benzodiazepines.\textsuperscript{38}

Yet there are hazards to this clinical practice. Concurrent benzodiazepine use in opioid users is not associated with improved symptoms; instead daily benzodiazepine users have reported higher pain severity and less coping with their pain.\textsuperscript{39} While benzodiazepines are primarily indicated for sleep and anxiety disorders, Lintzeris and Nielsen of the University of Sydney have written that the evidence for these clinical recommendations is primarily, “...confined to short-term controlled trials of up to several months duration in non-opioid-dependent populations, and long-term observational studies of [benzodiazepine] treatment for these indications are difficult to interpret due to imprecision in the differentiation of relapse, rebound, and withdrawal phenomena.”\textsuperscript{40} A clinical guideline from the American College of Physicians and the American Pain Society in 2007 highlighted that benzodiazepines are not FDA-approved for treating low back pain and highlighted the risk for addiction and misuse if used for more than short-term relief for acute or chronic back pain. The guideline recommended benzodiazepines should only be used for a time-limited course of therapy.\textsuperscript{41}

A second common clinical scenario is co-prescribing in the setting of co-existing psychiatric illness. Chronic pain patients using benzodiazepines frequently have comorbid mental health conditions. One study found that active benzodiazepine users were 50% more likely to have used antidepressants and three times more likely to have taken antipsychotic medication in the past month.\textsuperscript{42} According to the Treatment Episode Dataset, a national data system that captures all admissions to addiction treatment centers in the U.S., almost half (45.7 percent) of all patients admitted for combined opioid and benzodiazepine use in 2010 reported having a co-occurring psychiatric disorder.\textsuperscript{43} A black box warning will draw greater attention to the risks of combined use in this population.

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\textsuperscript{39} \textit{Ibid.}

\textsuperscript{40} Lintzeris N, Nielsen S. 2010, \textit{op. cit.}


\textsuperscript{42} Nielsen S, Lintzeris N, Bruno R., et al. 2015, \textit{op. cit.}

Alternative approaches to combined use of opioid analgesic and benzodiazepines include nonpharmacologic treatment modalities for pain such as manipulation therapy, physical therapy, and massage. Similarly, use of other medication classes, meditation, and cognitive behavioral therapy for anxiety and sleep disorders may reduce concurrent use of benzodiazepines in patients with chronic pain.\textsuperscript{44} A black box warning would help clinicians to consider alternatives to combined prescribing of opioids and benzodiazepines.

A black box warning would also lead specialty societies and others to focus on the risks of co-prescribing in their guidelines and educational programs to clinicians, supplementing existing measures to improve appropriate prescribing. In recent years, several clinical guidelines have been released advising providers and patients of the dangers of concurrent use. A CDC Brief assessing commonalities in recently-issued provider guidelines about opioids in chronic pain found the Utah State Clinical Guidelines on Prescribing Opioids for Treatment of Pain, the Washington State Agency Medical Directors Group Interagency Guideline on Opioid Dosing for Chronic Noncancer Pain, the Canadian Guideline for Safe and Effective Use of Opioids for Chronic Noncancer Pain, the New York City Department of Health and Mental Hygiene Opioid Prescribing Guidelines, and the American Society of Interventional Pain Physicians Guidelines for Responsible Opioid Prescribing in Chronic Noncancer Pain all recommended against co-prescription of benzodiazepines and opioids or urged caution or tapering one medication class.\textsuperscript{45} The December 2015 draft of draft guidelines from the CDC on opioids for chronic pain recommend against co-prescription whenever possible because “[c]oncurrent use is likely to put patients at greater risk for potentially fatal overdose.”\textsuperscript{46}

In January 2014, Institutes for Clinical Systems Improvement released an Acute Pain Assessment and Opioid Prescribing Protocol document for providers that specifically included benzodiazepine use in their ABCDPQRS Opioid risk assessment due to the increased risk of sedation and overdose with concurrent use leading to their clinical recommendation that

\textsuperscript{44} Gudin, JA, Mogali, S, Jones, JD, Comer, SD. Risks, Management, and Monitoring of Combination Opioid, Benzodiazepines, and/or Alcohol Use. Postgrad Med. 2013;125(4): 115–130.


“...patients using [benzodiazepines] and opioids should be counseled not to combine these medications...”

With these guidelines buttressed by a black box warning, clinicians will be more likely to review their patients’ medication lists, including medications prescribed by others, to avoid this potential hazard. A few examples of current risk assessment and mitigation tools include: the use of Prescription Drug Monitoring Programs, integration of appropriate urine drug tests into practice, increased consideration for non-opioid and non-pharmacological alternatives for pain management, and educational initiatives to increase provider awareness of Screening, Brief Intervention, and Referral to Treatment (SBIRT) initiatives and other referral resources.

A black box warning would enhance educational efforts by public health officials. In June 2014, the Maryland Department of Health and Mental Hygiene sent a letter to all licensed physicians warning of the "potentially lethal combination of benzodiazepines and opioids." Other states and localities are planning similar efforts.

V. EXISTING LABELING

Only a few labels and medication guides contain specific information on the dangers of concurrent use of these two classes of medications; none contain black box warnings.

_Opioids_. The labels or guides for buprenorphine, fentanyl, and methadone specifically mention the risk of concurrent use with benzodiazepines. For example, the buprenorphine label, in warnings, states, “A number of deaths have occurred when addicts have intravenously misused buprenorphine, usually with benzodiazepines concomitantly.” Suboxone (buprenorphine) also has a medication guide that informs patients about the risk of benzodiazepines, stating: “You have a higher risk of death and coma if you take Suboxone with other medications, such as benzodiazepines.” The label for methadone states, “Deaths associated with illicit use of methadone frequently have involved concomitant benzodiazepine abuse.” The medication guide for methadone, however, does not mention this risk. The labels and medication guides for other commonly prescribed opioids, including oxycodone,

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hydrocodone, and codeine, only make general and inconsistent mention of interactions with Central Nervous System (CNS) depressants and sedatives.

*Benzodiazepines.* There is scattered and inconsistent mention of potential problems with concurrent use of opioids on the labels of some benzodiazepine medications. For example, the label for midazolam states, in the interaction section, “the sedative effective….is accentuated by any concomitantly administered medication which depresses the central nervous system, particularly narcotics (e.g., morphine, meperidine and fentanyl)…” The label of diazepam states, in the precautions section, “If diazepam is to be combined with other psychotropic agents...careful consideration should be given to the pharmacology of the agents to be employed, particularly with known compounds which may potentiate the action of diazepam, such as....narcotics.” The medication guide for diazepam generically cautions against simultaneous use with alcohol and other CNS-depressant drugs.

Existing warnings on concurrent use of benzodiazepines and opioids are inconsistent, infrequent, and insufficient. They fail to reflect the strong biologic and epidemiological data on risks to patients of respiratory depression and fatal overdose from combining these classes of medications.

**VI. PUBLIC EDUCATION**

A black box warning would help patients recognize the risks of concurrent use of benzodiazepines and opioids and would emphasize the need to discard old or expired medications that could be otherwise combined with new prescriptions for dangerous effects. It would support education efforts aimed at informing the general public about the epidemic of fatal overdose and the importance of judicious prescribing.

**VII. POTENTIAL OBJECTIONS**

Some may object to class warnings when all possible combinations between opioids and benzodiazepines have not been fully studied. However, it is our view that the basic science and epidemiology support class effects that obviate the need for additional research. Moreover, clinicians and patients should generally be aware of the dangers; a strong black box warning will provide a clear general message to improve care and save lives.
VIII. FDA AUTHORITY

The Food and Drug Administration Amendments Act of 2007 (“FDAAA”), Section 901(a) of the FDAAA added Section 505(o)(4) to the FDCA, granted FDA authority to mandate post-approval safety-related labeling changes for both individual drugs and classes of drugs.49

IX. CONCLUSION

FDA guidance50 supports the use of black box warnings in several circumstances, including when:

● “There is an adverse reaction so serious in proportion to the potential benefit from (e.g., a fatal, life-threatening or permanently disabling adverse reaction) 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 severity by appropriate use of the drug (e.g., patient selection, careful monitoring, avoiding certain concomitant therapy, addition of another drug or managing patients in a specific manner, avoiding use in a specific clinical situation)”

Both of these conditions are met for the risk of fatal overdose from co-prescribing of benzodiazepines and opioids. Biological and epidemiological data support the urgency of action to warn prescribers and the public about this risk.

Based on this scientific record, we petition that the FDA:

1. Create and mandate black box warnings for all opioids and benzodiazepine class medications to read as follows:

   Labeling for all Opioid Class Medications should read:

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50 Food and Drug Administration 2011, op. cit.
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.

Labeling for all Benzodiazepine Class Medications should 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.

2. Require medication guides for both classes of medications that specifically warn patients of the potential dangers of combined use of opioids and benzodiazepines.

As physicians, public health officials, and researchers who have both analyzed the evidence and seen the impact of opioid overdose first-hand in our patients and loved ones, we urge the FDA to promptly consider these changes.

ENVIRONMENTAL IMPACT

According 1921 CPR Sec. 25.31(a), this Petition qualifies for a categorical exclusion from the requirement that an environmental impact statement be submitted.

ECONOMIC IMPACT

According to 21 CPR See 10.30(b)~ an economic impact statement is to be submitted only when requested by the Commissioner following reviewing of this Petition.
CERTIFICATION

The undersigned certifies that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petition that are unfavorable to the petition.

Respectfully submitted,

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