



WARNING LETTER

VIA UNITED PARCEL SERVICE AND E-MAIL

Ref.: [REDACTED]

[REDACTED]
Hennepin County Medical Center
Department of Emergency Medicine
701 Park Avenue, #MC-825
Minneapolis, Minnesota 55415-1623

Dear [REDACTED]:

This Warning Letter informs you of objectionable conditions observed during the U.S. Food and Drug Administration (FDA) inspection conducted at your clinical site between April 9 and April 23, 2019. Investigator Sharon Matson, representing FDA, reviewed your conduct of the following clinical investigations, which you performed as a sponsor-investigator:

- Protocol [REDACTED], "Prospective Observational Investigation of Olanzapine versus Haloperidol versus Ziprasidone versus Midazolam for the Treatment of Acute Undifferentiated Agitation in the Emergency Department," of the investigational drugs olanzapine, haloperidol, ziprasidone, and midazolam
- Protocol [REDACTED], "Prospective Observational Investigation of Olanzapine versus Midazolam for the Treatment of Acute Undifferentiated Agitation in the Emergency Department," of the investigational drugs olanzapine and midazolam

This inspection was conducted as a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to help ensure that the rights, safety, and welfare of human subjects have been protected.

At the conclusion of the inspection, Investigator Matson presented and discussed with you the Form FDA 483, Inspectional Observations. We acknowledge receipt of your May 14, 2019, written response to the Form FDA 483.

From our review of the FDA Establishment Inspection Report, the documents submitted with that report, and your written response dated May 14, 2019, it appears that you did not adhere

to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects. We wish to emphasize the following:

Failure to submit INDs for the conduct of clinical investigations with investigational new drugs subject to 21 CFR 312.2(a) [21 CFR 312.20 and 312.40(a)].

FDA regulations require a sponsor to submit, and to have in effect, an investigational new drug application (IND) before initiating a clinical investigation of a drug subject to 21 CFR 312.2(a) in human subjects, unless the clinical investigation qualifies for an exemption (see 21 CFR 312.20 and 312.40(a)). You failed to comply with these requirements. Specifically, you initiated and conducted the following clinical investigations of investigational drug products subject to section 505 of the Federal Food, Drug, and Cosmetic Act without submitting and having in effect an IND¹:

- The clinical investigation of the investigational drugs olanzapine, haloperidol, ziprasidone, and midazolam, conducted under Protocol [REDACTED]
- The clinical investigation of the investigational drugs olanzapine and midazolam, conducted under Protocol [REDACTED]

In your May 14, 2019, written response to the Form FDA 483, you stated that an IND was not needed for Protocol [REDACTED] or for [REDACTED] because the drugs administered in these clinical investigations were not research interventions. You stated that the Emergency Medicine (EM) physicians were free to use whichever therapy they thought was most appropriate using their professional medical judgment, and could choose not to enroll any particular subject in the investigations. You also stated that all of the drug products are part of the standard of care for sedation treatment.

In the alternative, you argued that if the clinical investigations were subject to FDA jurisdiction, they met the criteria at 21 CFR 312.2(b)(1) for exemption from the requirements of part 312. You argued that the investigations met all five criteria for the exemption. With respect to the third criterion, you stated that the investigation did not involve a route of administration, dosage level, use in patient population, or other factor that significantly increases the risk or decreases the acceptability of the risk to subjects because the drugs were used “essentially in accord with their approved labeling.” You also stated in your response that the EM physicians were well trained to care for these subjects receiving these drugs.

¹ Also, neither of these clinical investigations qualified for any of the exemptions listed at 21 CFR 312.2 from the application of 21 CFR part 312. Because you have argued that these clinical investigations were subject to the exemption provided at 21 CFR 312.2(b)(1), we discuss in more detail below the inapplicability of this provision to these clinical investigations.

We address both of your arguments below.

1. *Protocols [REDACTED] and [REDACTED] were clinical investigations of drugs as defined by 21 CFR 312.3(b).*

For the purposes of 21 CFR part 312, a clinical investigation is defined as “any experiment in which a drug is administered or dispensed to, or used involving, one or more human subjects. For the purposes of this part [312], an experiment is any use of a drug except for the use of a marketed drug in the course of medical practice” [21 CFR 312.3(b)].

The clinical investigations conducted under Protocols [REDACTED] and [REDACTED] involved the administration of olanzapine, haloperidol, ziprasidone, and midazolam, and of olanzapine and midazolam, respectively, to human subjects. Based on the information collected on inspection, Protocols [REDACTED] and [REDACTED] were designed to study the safety and efficacy of these drug products for the treatment of acute undifferentiated agitation in the Emergency Department (ED).

The use of these drug products was not “in the course of medical practice.” FDA has long held that when an investigator limits his choices, his patients’ choices, and the choices of the people working for him in the treatment of those patients, then he is conducting a clinical investigation. That is different from the practice of medicine, where the primary intent is to treat the individual patient.²

Both protocols pre-specified the drug intervention to be administered to agitated subjects requiring chemical sedation during specified time periods. This was reinforced by consistent communication from you, the sponsor-investigator, to ED personnel regarding the specific drugs that were to be administered on a given day. As such, the clinical investigations limited the ED physicians’ clinical judgment and limited the interventions available to ED physicians for administration to each subject.

For example:

- Protocol [REDACTED] stated: “All patients requiring chemical sedation for [sic] will receive olanzapine as the initial treatment for agitation for 21 days, followed by haloperidol as the initial treatment for agitation for 21 days, followed by ziprasidone as the initial treatment for agitation for 21 days, and finally midazolam as the initial treatment for agitation for 21 days All patients determined by the physician to require chemical sedation . . . will receive their initial intervention as a pre-specified medication [T]he clinical protocol will determine which medication the physician must order.” For Protocol [REDACTED], [REDACTED] 2017, [REDACTED] e-mailed Hennepin

² Indeed, FDA has provided guidance on this topic. See FDA’s guidance to industry *Investigational New Drug Applications (INDs) – Determining Whether Human Research Studies Can Be Conducted Without an IND* (published in September 2013), at 4, 15 (“For example, a randomized trial evaluating an unapproved use of a lawfully marketed drug is a clinical investigation and may require an IND. In contrast, use of a lawfully marketed drug for an unapproved use in the course of medical practice is not a clinical investigation and does not require an IND because it involves the use in an individual patient where the primary intent is to treat the patient”).

County Medical Center (HCMC) EM faculty, EM fellows, EM residents, EM physician assistants, and ED nurses, “Starting June 8 . . . [i]f you are planning to give the patient sedation, with this protocol, the **initial** medication given for **ANY** agitated patient in special care **MUST be the “Medication of the Week[”]** **Again, this medication of the week MUST be the first medication given to EVERY ED patient in special care for agitation** [emphasis in original].” The medication schedule was described in [REDACTED], with haloperidol starting on [REDACTED] ziprasidone starting on [REDACTED] olanzapine starting on [REDACTED] and midazolam starting on [REDACTED]. [REDACTED] sent similar e-mails on [REDACTED].

- Protocol [REDACTED] stated: “All patients requiring chemical sedation for[sic] will receive olanzapine as the initial treatment for agitation for 6 weeks, followed by midazolam as the initial treatment for agitation for 6 weeks. . . . All patients determined by the physician to require chemical sedation will receive their initial intervention as a pre-specified medication. . . . [T]he clinical protocol will determine which medication the physician must order.” For Protocol [REDACTED], on [REDACTED] [REDACTED] e-mailed HCMC EM residents and EM physician assistants, “If you are planning to give a patient medication in special care, the **initial** medication given for **ANY** agitated patient in special care **MUST be the “Medication of the Week”**. [sic] **This medication of the week MUST be the first medication given to EVERY ED patient in special care for agitation** [emphasis in original].” The medication schedule was described in the e-mail, with olanzapine starting on [REDACTED] and midazolam starting on [REDACTED].

Consequently, the investigations conducted under Protocols [REDACTED] and [REDACTED] [REDACTED] were clinical investigations of the investigational drugs olanzapine, haloperidol, ziprasidone, and midazolam, and of olanzapine and midazolam, respectively.³ Under 21 CFR 312.20 and 312.40, you were required to submit and to have in effect INDs before initiating these clinical investigations.

Your statements that the drugs studied in Protocol [REDACTED] and Protocol [REDACTED] [REDACTED] were not investigational drugs are not persuasive because they are inconsistent with the design and conduct of the clinical investigations. The clinical investigations involved the prospective administration of specific drug products depending on the date of administration, the assessment and documentation of time to sedation, and the comparison of times to sedation among different drugs where the investigational drug was the independent variable of primary interest. Contrary to your assertions, both clinical trials required the EM physicians to administer a specific investigational drug to agitated subjects who were to be sedated chemically. Whether an agitated subject in need of sedation received olanzapine, haloperidol, ziprasidone, or midazolam while Protocol [REDACTED] was ongoing, or whether an agitated subject in need of sedation received either olanzapine or midazolam while Protocol [REDACTED] was ongoing, depended not on the clinical judgment of the EM physicians but on the date the EM physicians encountered the subject. In addition, the presence of the choice not to enroll any particular subject is

³ We note that, for the same reason, these clinical investigations do not qualify for the exemption from the application of 21 CFR part 312 provided at 21 CFR 312.2(d).

common in clinical investigations and does not support your assertion that the drug products were not investigational new drugs with regard to subjects who were enrolled. Finally, the fact that the drugs individually can be part of standard of care does not render them non-interventions in the study setting, as was the case here, where the protocols pre-specified the drug intervention to be administered to agitated subjects requiring chemical sedation, and limited the EM physicians' clinical judgment and the interventions available to EM physicians for administration to each subject.

2. *The clinical investigations conducted under Protocols [REDACTED] and [REDACTED] are subject to the IND regulations under 21 CFR 312.2 and do not meet the exemption criteria under 21 CFR 312.2(b)(1).*

As noted above, FDA regulations require a sponsor to submit an IND before conducting a clinical investigation of a drug in human subjects, unless the clinical investigation qualifies for an IND exemption under 21 CFR 312.2(b). Under 21 CFR 312.2(b)(1), the clinical investigation of a lawfully marketed drug product in the United States is exempt from the IND regulations for a clinical investigation if **all** of the following exemption criteria are met:

1. The investigation is not intended to be reported to FDA as a well-controlled study in support of a new indication for use, and there is no intent to use the investigation to support any other significant change in the labeling of the drug.
2. In the case of a lawfully marketed prescription drug, the investigation is not intended to support a significant change in the advertising for the drug.
3. The investigation does not involve a route of administration, dosage level, use in a patient population, or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product.
4. The investigation is conducted in compliance with the requirements for institutional review set forth in 21 CFR part 56 and with the requirements for informed consent set forth in 21 CFR part 50.
5. The investigation is conducted in compliance with the requirements of 21 CFR 312.7.

Your use of the investigational drugs (olanzapine, haloperidol, ziprasidone, and midazolam) in the clinical investigations conducted under Protocols [REDACTED] and [REDACTED] did not qualify for the exemption at 21 CFR 312.2(b)(1). For example, these investigations did not satisfy the third exemption criterion above, found at 21 CFR 312.2(b)(1)(iii). That is to say, the investigations significantly increased the risks (or decreased the acceptability of the risks) associated with the use of the drug products.

Here, the clinical investigations conducted under Protocols [REDACTED] and [REDACTED] involved the administration of investigational new drugs in populations that significantly increased the risks (or decreased the acceptability of the risks) associated

with the use of the drug products.⁴ First, neither study excluded subjects taking medications known to have drug-drug interactions with the investigational drugs, such as inhibitors or inducers of CYP450 enzymes. Second, neither study excluded subjects with liver or kidney dysfunction, despite the fact that the investigational drugs are known to be influenced by these impairments. As such, these clinical investigations failed to meet the exemption criteria under 21 CFR 312.2(b)(1)(iii).

We note that on [REDACTED] 2017, you submitted [REDACTED] for the investigational drugs olanzapine, haloperidol, ziprasidone, and midazolam in order to conduct a clinical trial that would have been substantially similar to the trial you sponsored and conducted under Protocol [REDACTED]. In a [REDACTED] 2017, teleconference with you, the Division of Psychiatry Products (DPP) placed [REDACTED] on Full Clinical Hold. In addition, DPP issued you a letter dated [REDACTED] 2017, that explained the basis for the hold and detailed recommendations to address the deficiencies with [REDACTED]. Among other things, DPP's letter specifically recommended that subjects with organ (liver or kidney) dysfunction and subjects taking medications with a known interaction with the study drugs be excluded from the study, based on risks of subject safety due to the proposed investigational drugs.

Instead of addressing these deficiencies, you proceeded with a substantially similar clinical investigation of the investigational drugs olanzapine, haloperidol, ziprasidone, and midazolam under Protocol [REDACTED], and a follow-up trial of investigational drugs olanzapine and midazolam under Protocol [REDACTED], without submitting or having in effect an IND. Moreover, neither Protocol [REDACTED] nor [REDACTED] addressed the concerns DPP had communicated to you regarding the exclusion of these subjects from the study populations, based on the known risks of the investigational drugs.

Because the administration of the investigational drugs (olanzapine, haloperidol, ziprasidone, and midazolam) in these clinical investigations significantly increased the risks and/or decreased the acceptability of the risks associated with the use of these drug products, the exemption criterion at 21 CFR 312.2(b)(1)(iii) was not met, and you were required to submit and have in effect INDs before initiating these clinical investigations.

In your May 14, 2019, response, you stated that the use of the investigational drugs did not significantly increase the risk or decrease the acceptability of the risk to subjects because the drugs were used "essentially in accord with their approved labeling." Your statement is factually incorrect, because none of the four drugs used in Protocols [REDACTED] and [REDACTED] is indicated to treat acute undifferentiated agitation. In any case, your response did not address the fact that study subjects were at significantly increased

⁴ See FDA's guidance to industry *Investigational New Drug Applications (INDs)—Determining Whether Human Research Studies Can Be Conducted Without an IND* (published in September 2013), at 7 (specifically stating that, when considering whether the risk associated with a drug product is significantly increased or the acceptability of the risk is significantly decreased for purposes of 21 CFR 312.2(b)(1)(iii), a population chosen for study could be at increased risk because of decreased renal or hepatic function or because of concomitant therapy).

risk because subjects who should have been excluded from the studies for safety reasons, as DPP had indicated, were not excluded. You also stated in your response that the EM physicians were well trained to care for these subjects receiving these drugs. This, however, does not change the fact that the investigations, by failing to exclude study subjects at significantly increased risk from administration of the investigational drugs, significantly increased the risks or decreased the acceptability of the risks to subjects.

This letter is not intended to be an all-inclusive list of deficiencies with your clinical study of an investigational drug. It is your responsibility to ensure adherence to each requirement of the law and relevant FDA regulations. You should address these deficiencies and establish procedures to ensure that any ongoing or future studies comply with FDA regulations.

This letter notifies you of our findings and provides you an opportunity to address the deficiencies noted above. Within 15 business days of your receipt of this letter, you should notify this office in writing of the actions you have taken to prevent similar violations in the future. Failure to address this matter adequately may lead to regulatory action. If you believe that you have complied with the Federal Food, Drug, and Cosmetic Act and FDA regulations, include your reasoning and any supporting information for our consideration.

If you have any questions, please contact Sherry G. Bous, Pharm.D., at 240-402-8176 or CDER-OSI-Communications@fda.hhs.gov. Your written response and any pertinent documentation should be addressed to:

Sherry G. Bous, Pharm.D.
Director
Division of Enforcement and Postmarketing Safety
Office of Scientific Investigations
Office of Compliance
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Building 51, Room 5364
10903 New Hampshire Avenue
Silver Spring, MD 20993

Sincerely yours,

David Burrow

-S

David C. Burrow, Pharm.D., J.D.
Director
Office of Scientific Investigations
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Digitally signed by David Burrow -S
DN: c=US, o=U.S. Government, ou=HHS,
ou=FDA, ou=People, cn=David Burrow -S,
0.9.2342.19200300.100.1.1=2000334433
Date: 2021.05.05 12:08:16 -0400

cc:

[REDACTED]

June 4, 2021

Sherry G. Bous, Pharm.D.
Director
Division of Enforcement and Postmarketing Safety
Office of Scientific Investigations
Office of Compliance
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Building 51, Room 5364
10903 New Hampshire Avenue
Silver Spring, MD 20993

Re: Response to Warning Letter
Ref: [REDACTED]

Confidential¹

Dear Director Bous:

This correspondence is in response to the Warning Letter dated May 5, 2021, regarding the inspection by the U.S. Food and Drug Administration (FDA) at Hennepin Healthcare System, Inc. ("Hennepin Healthcare") between April 9 and April 23, 2019, reviewing the conduct of two clinical research studies, [REDACTED] and [REDACTED].² In the Warning Letter, FDA explains its view that the conduct of these studies fell within FDA's jurisdiction due to the investigational use of lawfully marketed drug products, and that an Investigational New Drug Application (IND) was required under the Federal Food, Drug, and Cosmetic Act and FDA's implementing regulations at 21 CFR Part 312 to conduct these studies. FDA further explains why the studies did not meet the exemption criteria under 21 CFR 312.2(b)(1), specifically that the use of the drug products in the studies significantly increased the risks (or decreased the acceptability of the risks) associated with the use of the drug products.

I want to note at the outset that the issuance of the Warning Letter itself seems to suggest significant, imminent harm to study participants as described in FDA's Regulatory Procedures Manual.³ Just to be clear, [REDACTED] was approved by Hennepin Healthcare's Institutional Review Board (IRB) in May 2017 and was closed in June of 2018, and [REDACTED] was approved

¹ This document contains confidential commercial, trade secret, and personal privacy information that is protected from public disclosure under the Federal Food, Drug, and Cosmetic Act, the Freedom of Information Act, FDA's implementing regulations, and the Trade Secrets Act. In accordance with FDA's implementing regulations, if a request for disclosure is received, or if for any other reason FDA believes that any portion of this document must be disclosed publicly, I ask that I be notified and provided an opportunity to address why the information or materials should not be released.

² I received an extension to submit this Warning Letter response beyond FDA's original 15 day deadline from [REDACTED] CDER Compliance's Division of Scientific Investigations, [REDACTED]. The newly agreed upon deadline was Friday, June 4, 2021.

³ FDA, Regulatory Procedures Manual, Chapter 4 (at 4-1-1), available at: <https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/compliance-manuals/regulatory-procedures-manual>.

by the IRB in May of 2018, was paused in July of 2018, and was closed in November 2018. Thus, no study participants are currently enrolled in either study, and none have been for several years. Therefore there is no current or ongoing significant or imminent harm to any study subjects in connection with [REDACTED] and [REDACTED]. Further, as explained in more detail below, both Hennepin Healthcare and I have implemented numerous and significant changes to better our understanding of FDA's human subjects protections and clinical trial requirements to ensure that all research subjects are appropriately protected.

Please know that I recognize and completely understand the importance of complying with FDA's investigational new drug and human subjects protections regulations to safeguard both clinical trial participants and the integrity of the data. I was a resident and fellow at the time and I undertook these IRB approved studies with guidance from my mentors with the intention of contributing to evidence-based medicine in the emergency department setting and ultimately improving the emergency care provided to our patients. Although it is no excuse, at no time did I intend to, nor believed I was, violating the IND regulations. I now fully understand FDA's position and regret not having conducted the studies in compliance with FDA's statute and regulations.

Conducting research in the emergency department with agitated patients is very challenging, and involves complex circumstances. Because the drug products used in [REDACTED] and [REDACTED] were approved drug products, and administration of those products to agitated patients was part of our hospital's standard of care, I mistakenly thought at the time that the drug products were not research-related interventions and an IND was not needed. I now understand that the drugs were part of the research based on the study design and that the studies should have been conducted under an IND.

I have taken numerous remedial steps to ensure that the violations described by FDA in the Inspectional Observations (Form FDA 483) and the Warning Letter do not occur in the future.

- **Training:**

- I completed the comprehensive investigator retraining offered by Hennepin Healthcare on May 7 and May 8, 2019, to refresh and reinforce my understanding of the regulatory requirements surrounding the conduct of clinical research. I also continue to keep all CITI and other formal training modules up to date.
- I voluntarily undertook a review of all completed studies where I was a co-investigator to add to my learning about protocols, procedures, documentation completeness, and organizational structure that occurred in other unrelated work. While these were not federally regulated studies, I felt the exercise was informative and educational for me as I considered the findings in FDA's Form 483.
- I intend to undertake additional training including the OHRP Human Research Protection Training and the Protecting Human Research Participants (PHRP) Training.

- **Mentoring:**

- I conducted regular formal mentorship meetings with [REDACTED] to review the [REDACTED] and [REDACTED] studies, to review inactive protocols as an additional educational opportunity, and to discuss considerations of any future research work. Also, throughout this process, I continued to meet with [REDACTED] and other senior researchers at Hennepin Healthcare, as well as [REDACTED] of the [REDACTED]. My commitment to mentorship has involved active engagement with individuals from within and outside Hennepin Healthcare for support and guidance.

- **Limited Research**

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- Due to a multitude of considerations, I have redirected much of my professional focus since 2019 on clinical and administrative work.
- In light of the Warning Letter, I commit to never again conduct research with a research design similar to [REDACTED] and [REDACTED]. In addition, I have no current plans to participate in federally regulated research in the future and intend only to engage in retrospective chart review work as a co-investigator.

In addition, it is my understanding that my former employer, Hennepin Healthcare, has taken, and continues to undertake, numerous steps to strengthen its clinical research program institution-wide, to create a culture of compliance and to engage in research-related community outreach. To my knowledge, Hennepin Healthcare has:

- implemented the use of standardized protocol templates for all investigator-initiated clinical studies to ensure accurate and complete submissions to the IRB;
- required institutional pre-review of all IRB submissions that involve investigator-initiated clinical studies; this review includes an assessment of whether an IND or Investigational Device Exemption (IDE) is required;
- re-educated IRB members, hospital staff, and clinical researchers on the proper and compliant conduct of clinical research;
- instituted mandatory clinical research, human subjects protections, and Good Clinical Practice education for all new research staff;
- added required training on cultural competency and implicit bias for all research staff;
- instituted the use of new checklists and guidance documents for the IRB and investigators to help ensure compliance, and updated the IRB's written procedures accordingly;
- implemented an electronic IRB management system to facilitate compliant IRB review and processes;
- developed a Public Research Advisory Board comprised of diverse experts, community leaders, and former research subjects, to improve community outreach and engagement;
- established a Community Advisory Board (CAB) to function as an advisory group of volunteer members who are representative of the patient community; CAB is focused on relationship building and partnering with community organizations, populations with disproportionate unmet health needs, the business community and the individuals who live in the community; and
- developed in-hospital and online information mechanisms to notify patients and others in the community about the research being conducted by hospital physicians/researchers.

All of these corrective actions were/are designed to prevent the violations listed in the Form FDA 483 and the Warning Letter in order to better protect the health and safety of research study participants. I fully understand the importance of regulatory compliance and will never again conduct FDA-regulated clinical research without an IND, and will never conduct any future studies with a similar design. In addition, upon reading FDA's Warning Letter, I fully understand that [REDACTED] and [REDACTED] changed the levels of risk to participants associated with the marketed drug products used in the studies, and thus why the IND exemption criteria were not met.

To reiterate, I understand it is my responsibility to ensure adherence to the law and FDA regulations in the conduct of clinical research to protect the safety and welfare of research participants. I also understand that I failed to comply with the regulations in my conduct of [REDACTED] and [REDACTED] by not having an IND and by not meeting the IND exemption criteria. I and Hennepin Healthcare have undertaken and continue to take extensive corrective actions to prevent any future noncompliance. I appreciate your consideration of my response and the opportunity to address my deficiencies. I hope this response is adequate in addressing the Agency's concerns and that this response facilitates closure of this matter at this time. Please do not hesitate to contact me at [REDACTED]

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[REDACTED] if you have any questions or [REDACTED] [REDACTED] at
[REDACTED] for questions related to steps taken by Hennepin Healthcare

Sincerely,

[REDACTED]