DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

Jasmine Shah, Vice President
Regulatory and Medical Affairs
Alvogen, Inc.
10 Bloomfield Ave
Pine Brook, NJ 07058

RE: ANDA 091681
Disulfiram Tablets, USP
MA #1

Dear Mr. Shah:

The Office of Prescription Drug Promotion (OPDP) of the U.S. Food and Drug Administration (FDA) has reviewed a "New Product Release – Notification Disulfiram Tablets USP, 250 mg in printed sales aid" (sales aid) for Disulfiram Tablets, USP (Disulfiram) submitted by Alvogen, Inc. (Alvogen) under cover of Form FDA 2253. This sales aid is misleading because it makes representations about the efficacy of Disulfiram but fails to communicate any risk information associated with its use and it omits material facts. Thus, the sales aid misbrands Disulfiram within the meaning of the Federal Food, Drug, and Cosmetic Act (FD&C Act), and makes its distribution violative. 21 U.S.C. 352(a); 321(n); 331(a); 21 CFR 1.21(a). *Cf.* 21 CFR 202.1(e)(5).

Background

Below are the indication and summary of the most serious and most common risks associated with the use of Disulfiram.[1] According to the INDICATIONS AND USAGE section of the FDA-approved product labeling (PI):

> Disulfiram is an aid in the management of selected chronic alcohol patients who want to remain in a state of enforced sobriety so that supportive and psychotherapeutic treatment may be applied to best advantage.
>
> Disulfiram is not a cure for alcoholism. When used alone, without proper motivation and supportive therapy, it is unlikely that it will have any substantive effect on the drinking pattern of the chronic alcoholic.

Disulfiram is associated with a number of serious risks, some of which are potentially fatal, including a Boxed Warning regarding the administration of Disulfiram. Disulfiram is

[1] This information is for background purposes only and does not necessarily represent the risk information that should be included in the promotional piece cited in this letter.

contraindicated in patients who are receiving or have recently received metronidazole, paraldehyde, alcohol or alcohol-containing preparations as well as in the presence of severe myocardial disease or coronary occlusion, psychoses, and hypersensitivity to disulfiram or to other thiuram derivatives. The PI contains Warnings pertaining to the disulfiram-alcohol reaction. In addition, the PI includes Precautions regarding the use of identification cards for patients under disulfiram treatment, dependence and abuse, hepatic toxicity, and patient exposure to ethylene dibromide.

The Adverse Reactions section of the PI indicates that optic neuritis, peripheral neuritis, polyneuritis and peripheral neuropathy may occur following administration of Disulfiram. Multiple cases of hepatitis, occasional skin eruptions, transient mild drowsiness, fatigability, impotence, headache, acneform eruptions, allergic dermatitis, a metallic or garlic-like aftertaste and psychotic reactions have also been reported with the administration of Disulfiram.

Omission of Risk Information

Promotional materials are misleading if they fail to reveal facts that are material in light of the representations made by the materials or with respect to consequences that may result from the use of the drug as recommended or suggested by the materials. The sales aid includes claims such as (bolded emphasis original):

- "Indications and Usage: Disulfiram is an aid in the management of selected chronic alcohol patients who want to remain in a state of enforced sobriety so that supportive and psychotherapeutic treatment may be applied to best advantage."
- "Product Category: **Alcohol antagonist**"

The sales aid is misleading because it makes representations about the efficacy of Disulfiram, but fails to communicate **any** of the risks associated with its use. This omission of risk information is particularly concerning considering that the Disulfiram PI includes a Boxed Warning. By omitting the most serious and frequently occurring risks associated with Disulfiram, the sales aid misleadingly suggests that Disulfiram is safer than has been demonstrated.

Omission of Material Fact

The sales aid includes the following claim regarding Disulfiram's use for the treatment of alcoholism:

- "Indications and Usage: Disulfiram is an aid in the management of selected chronic alcohol patients who want to remain in a state of enforced sobriety so that supportive and psychotherapeutic treatment may be applied to best advantage."

The sales aid is misleading because it fails to communicate material information from Disulfiram's full FDA-approved indication for the management alcoholism. According to the Indications and Usage section of the PI, "Disulfiram is not a cure for alcoholism. When used alone, without proper motivation and supportive therapy, it is unlikely that it will have any substantive effect on the drinking pattern of the chronic alcoholic."

Conclusion and Requested Action

For the reasons discussed above, the sales aid misbrands Disulfiram within the meaning of the FD&C Act, and makes its distribution violative. 21 U.S.C. 352(a); 321(n); 331(a); 21 CFR 1.21(a). *Cf.* 21 CFR 202.1(e)(5).

OPDP requests that Alvogen immediately cease violating the FD&C Act, as discussed above. Please submit a written response to this letter on or before May 20, 2014, stating whether you intend to comply with this request, listing all promotional materials (with the 2253 submission date) for Disulfiram that contain presentations such as those described above, and explaining your plan for discontinuing use of such materials.

Please direct your response to the undersigned at the **Food and Drug Administration, Center for Drug Evaluation and Research, Office of Prescription Drug Promotion, 5901-B Ammendale Road, Beltsville, Maryland 20705-1266** or by facsimile at (301) 847-8444. To ensure timely delivery of your submissions, please use the full address above and include a prominent directional notation (e.g. a sticker) to indicate that the submission is intended for OPDP. Please refer to MA # 1 in addition to the ANDA number in all future correspondence relating to this particular matter. All correspondence should include a subject line that clearly identifies the submission as a Response to Untitled Letter. OPDP reminds you that only written communications are considered official.

The violations discussed in this letter do not necessarily constitute an exhaustive list. It is your responsibility to ensure that your promotional materials for Disulfiram comply with each applicable requirement of the FD&C Act and FDA implementing regulations.

Sincerely,

{See appended electronic signature page}

L. Shenee' Toombs, Pharm.D.
Regulatory Review Officer
Office of Prescription Drug Promotion

{See appended electronic signature page}

Samuel M. Skariah, Pharm.D.
Team Leader
Office of Prescription Drug Promotion

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

LATOYA S TOOMBS
05/06/2014

SAMUEL M SKARIAH
05/06/2014