U.S. FOOD & DRUG ADMINISTRATION

10903 New Hampshire Avenue
Silver Spring, MD 20993

Via UPS **Warning Letter** 320-17-45

August 2, 2017

Michele Boisvert
Chief Executive Officer
Homeolab USA Inc.
(Part of the parent company, Homeocan Inc.)
3025 De L'Assomption Blvd.
Montreal, QC, Canada, H1N 2H2

Dear Ms. Boisvert:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Homeolab USA Inc. (part of the parent company, Homeocan Inc.) at 3025 De L'Assomption Blvd., Montreal, Québec, from January 9 to 13, 2017.

This warning letter summarizes significant violations of current good manufacturing practice (CGMP) regulations for finished pharmaceuticals. See 21 CFR, parts 210 and 211.

Because your methods, facilities, or controls for manufacturing, processing, packing, or holding do not conform to CGMP, your drugs are adulterated within the meaning of section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 351(a)(2)(B).

We reviewed your January 26, 2017, response in detail and acknowledge your subsequent correspondence.

During our inspection, our investigator observed specific violations including, but not limited to, the following.

1. Your firm failed to establish and follow adequate control procedures to monitor the output and to validate the performance of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the drug product (21 CFR 211.110(a)).

Your firm released multiple lots of homeopathic in-process powder blends prior to attempting to validate your manufacturing process. You manufacture **(b)(4)** homeopathic in-process powder blend mixtures which you send to Raritan Pharmaceuticals Inc. (Raritan), a contract manufacturing organization, to produce finished homeopathic drug products for the United States (U.S.) market. Some of your powder blend mixtures are manufactured from ingredients that pose potentially toxic effects. For example, your Infants' Teething Tablet **(b)(4)** contains belladonna. Raritan uses this powder blend mixture to produce finished drug products for infants and children, a population vulnerable to the toxic effects of belladonna. You shipped **(b)(4)** lot **(b)(4)** of Infants' Teething Tablet **(b)(4)** to the U.S. market before evaluating whether your manufacturing process was reliable and reproducible.

Your operators use a **(b)(4)**, an inherently variable process, to **(b)(4)** produce in-process powder blends, including those made from toxic ingredients. You did not test the in-process powder blends for adequacy of mixing to assure uniformity and homogeneity prior to release and shipment to your contract manufacturer, Raritan.

FDA collected samples of your in-process drugs (**(b)(4)** lot **(b)(4)**) during our September-October 2016 inspection of Raritan. FDA analyses indicated that your in-process drugs were not homogeneous in composition.

Raritan used your powder blends to contract manufacture adulterated finished drug products that you marketed for use in infants and children in the United States. FDA analysis of finished drug products made from your in-process blends also demonstrated non-homogeneous composition. We acknowledge that the teething tablets made from your non-uniform powder blends were recalled.

We also note that during the inspection of your facility, you provided a validation report initiated two weeks after we contacted you to schedule the inspection. However, your process validation does not adequately address potential sources of variation or critical parameters that should be monitored and controlled in order to produce drugs of uniform character and quality. For example:

- You have not validated the uniformity of active ingredients in your in-process drugs. You use **(b)(4)** solution as a surrogate for the active ingredients, rather than validating the actual processes. There is no scientific justification for use of **(b)(4)**. It has not been demonstrated to have the same physicochemical properties and mixing characteristics as the actual drug ingredients mixed in your process.
- Your manufacturing instructions are not well specified.
- The validation protocol and analysis lack well defined acceptance criteria and sufficiently detailed parameters (e.g. particle size, endpoints of **(b)(4)**) to ensure that your manufacturing process is reliable and reproducible.
- Your protocol explicitly refers to "the person being validated." If the results are not compliant, the person can then be "subjected to new validations." Your process validation appears to be used as trial runs to evaluate people and lacks sufficient focus on ensuring that the process itself, as designed, is adequate to enable reproducibility.

Your firm lacks adequate written procedures that establish an ongoing program for monitoring process control and detecting variation to ensure maintenance of a stable manufacturing operation. Reliable manufacturing operations are essential to ensure consistent drug quality throughout each batch. When

significant variability is observed in one or more stages of pharmaceutical production, it is essential that executive management support and implement effective actions to address the source(s) of the variation and provide for a continued state of control.

In response to this letter, we request that you provide:

- A data-driven and scientifically sound program that identifies and controls all sources of variability, such that your in-process powder blend mixtures will consistently meet appropriate quality attributes. This includes, but is not limited to, evaluating suitability of equipment for its intended use, assuring quality of input materials, and determining the capability of each manufacturing process step and control.
- A risk assessment for distributed drug products manufactured with in-process powder blend mixtures produced by an un-validated process. Your risk assessment should address any such products intended for vulnerable populations, distributed within the United States, and still within expiry.

Refer to the FDA 2011 guidance for industry, *Process Validation: General Principles and Practices* at https://www.fda.gov/downloads/drugs/guidances/ucm070336.pdf.

2. Your firm failed to test samples of each component for identity and conformity with all appropriate written specifications for purity, strength, and quality (21 CFR 211.84(d)(1) and (2)).

Our inspection findings indicate that you do not perform appropriate identity testing for the components that you use in your drug manufacturing process (e.g., belladonna **(b)(4)**). You also do not test or appropriately validate test results for the purity, strength, and quality of these components. By not adequately analyzing your components for identity, purity, strength, and quality, you failed to ensure the suitability of incoming raw materials for processing.

In your response, you said that you "perform testing according to the requirements of the Homeopathic Pharmacopeia, which are used to identify the **(b)(4)**…." The Homeopathic Pharmacopeia of the United States (HPUS) requires multiple analytical identity tests. Your response failed to adequately describe whether each lot of components will be fully and appropriately tested for identity prior to use in manufacturing, and whether other attributes will also be tested.

Furthermore, in your response dated June 7, 2017, you said that you accept "incoming material receipts on the basis of the supplier's Certificate of Analysis." Also, the SOP you provided, "Supplier certification Procedure," indicates that the quality unit must assure that the supplier's analytical results comply with the HPUS, internal specifications, or the "HAB/GAP." Your response and SOP do not clearly indicate that validation of suppliers' certificates of analysis will occur at appropriate intervals to ensure that results (e.g., assay for alkaloids) continue to be reliable. Provide adequate scientific justification for how you will assure that components that pose potentially toxic effects meet appropriate specifications before use in operations. Include remediation of your supplier qualification procedure (e.g., clearly predefined specifications, periodic revalidation).

Also, we request that you provide a risk assessment for any drug product lots manufactured using components which were not adequately tested and controlled. Your risk assessment should address all

products within expiry and distributed within the United States, and place particular emphasis on those intended for infants and children.

Contract Agreements

Your quality agreement with your contract manufacturing organization, Raritan, **(b)(4)**. Note that when a manufacturer employs a contract facility for part of drug manufacturing (including processing, packing, holding, or testing), the manufacturer's quality unit is responsible for approving or rejecting drug products manufactured by the contract facility, **(b)(4)**. See 21 CFR 200.10(b) and 211.22(a). Furthermore, it is important to note that quality agreements cannot be used to delegate statutory or regulatory responsibilities to comply with CGMP. Refer also to the FDA 2016 guidance for industry, *Contract Manufacturing Arrangements for Drugs: Quality Agreements*, at https://www.fda.gov/downloads/drugs/guidances/ucm353925.pdf.

Limiting Photography

During the inspection, our investigator attempted to take pictures of excess material clinging to the sides of the **(b)(4)** used in the **(b)(4)** of drugs intended for U.S. distribution. Your consultant impeded the inspection by preventing our investigator from photographing this piece of equipment.

When an owner, operator, or agent delays, denies, limits, or refuses an inspection, the drugs may be deemed adulterated under section 501(j) of the FD&C Act. See FDA's guidance document, *Circumstances that Constitute Delaying, Denying, Limiting, or Refusing a Drug Inspection*, at https://www.fda.gov/downloads/regulatoryinformation/guidances/ucm360484.pdf.

CGMP Consultant Recommended

Based upon the nature of the violations we identified at your firm, we strongly recommend engaging a consultant qualified in 211.34 to assist your firm in meeting CGMP requirements. Your use of a consultant does not relieve your firm's obligation to comply with CGMP. Your firm's executive management remains responsible for fully resolving all deficiencies and ensuring ongoing CGMP compliance.

Relationship between Homeolab USA, Inc. and Parent Company Homeocan, Inc.

In your response you state, "Homeolab is NOT a manufacturer. Homeolab is a private label distributor, which has no manufacturing capabilities." In your response you also state, "Homeocan is by agreement a contract manufacturer for Homeolab."

Homeolab USA Inc. and Homeocan Inc. share the same address, facility, and personnel, including the chief executive officer and the head of quality. Your head of quality signs email correspondence with "Homeocan Inc./Homeolab USA" as your firm's identity. Homeolab (part of the parent company, Homeocan Inc.) is a registered manufacturer with the FDA. According to your *Duties and Responsibilities* document, Homeolab is responsible for "GMP Compliance with regulatory bodies" and "Approval of Batch for Distribution." In terms of drug manufacturing, Homeolab USA Inc. and

Homeocan Inc. have no significant separation, so we are treating Homeolab/Homeocan as a single entity.

Conclusion

Violations cited in this letter are not intended as an all-inclusive list. You are responsible for investigating these violations, for determining the causes, for preventing their recurrence, and for preventing other violations.

FDA placed your firm on Import Alert 66-40 on May 3, 2017.

Until you correct all violations completely and we confirm your compliance with CGMP, FDA may withhold approval of any new applications or supplements listing your firm as a drug manufacturer.

Failure to correct these violations may also result in FDA continuing to refuse admission of articles manufactured at Homeolab/Homeocan, 3025 De L'Assomption Blvd., Montreal, Québec, into the United States under section 801(a)(3) of the FD&C Act, 21 U.S.C. 381(a)(3). Under this authority, articles may be subject to refusal of admission, in that the methods and controls used in their manufacture do not appear to conform to CGMP within the meaning of section 501(a)(2)(B) of the FD&C Act, 21 U.S.C. 351(a)(2)(B).

After you receive this letter, respond to this office in writing within 15 working days. Specify what you have done since our inspection to correct your violations and to prevent their recurrence. If you cannot complete corrective actions within 15 working days, state your reasons for delay and your schedule for completion.

Send your electronic reply to CDER-OC-OMQ-Communications@fda.hhs.gov or mail your reply to:

Matthew Schnupp
Consumer Safety Officer
U.S. Food and Drug Administration
White Oak Building 51, Room 4359
10903 New Hampshire Avenue
Silver Spring, MD 20993
USA

Please identify your response with FEI 1000399435.

Sincerely,
/S/
Thomas J. Cosgrove, J.D.
Director
Office of Manufacturing Quality
Office of Compliance
Center for Drug Evaluation and Research