U.S. Food & Drug Administration
Division of Pharmaceutical Quality
Operations I
New Jersey District
10 Waterview Boulevard, 3rd Floor
Parsippany, NJ 07054

WARNING LETTER
17-NWJ-09

June 20, 2017

VIA UNITED PARCEL SERVICE

Dr. Vin K. Nayak
President
Raritan Pharmaceuticals, Inc.
8 Joanna Court
East Brunswick, NJ 08816

Dear Dr. Nayak,

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Raritan Pharmaceuticals, Inc. at 8 Joanna Court, East Brunswick, New Jersey, from September 29 to October 20, 2016.

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 drug products 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).

In addition, based on our review of the labeling, "Homeopathic Infant's Teething Tablets" is a misbranded drug in violation of sections 502 and 301(a) of the FD&C Act, 21 U.S.C. 352 and 331(a).

We reviewed your November 3, 2016, response in detail, and acknowledge your subsequent correspondence.

During our inspection, our investigators observed specific violations including, but not limited to, the following:

CGMP Violations

1. 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)(2))

You manufacture Infants' Teething Tablets from ingredients that pose potential toxic effects. Specifically, this drug product contains belladonna and is marketed for vulnerable patient populations, including infants and children under two years of age. You do not sample and test all components of your homeopathic drug products for conformity with all appropriate written specifications for purity, strength, and quality, or, for components for which a report of analysis is provided by the supplier, in lieu of such testing, you do not conduct at least one specific identity test for such components.

For example, you failed to test **(b)(4)** received from **(b)(4)** (part of the parent company,**(b)(4)**.) for any quality criteria, including identity, prior to use in production. In addition, our inspection found that some components, for which you did not conduct testing for conformity with appropriate written specifications, were received without a certificate of analysis, including:

- **(b)(4)**, Lot **(b)(4)**
- **(b)(4)**, Lot **(b)(4)**

FDA sampled the **(b)(4)** Lot **(b)(4)** at your facility, and found that the material was not homogenous in composition and exhibited high variability, which render it of unacceptable quality. Because the component was not of uniform character and quality, it should not have been released for use in the manufacture of drug products. This variability exposes infants and children who are given your drugs to potentially significant safety hazards from belladonna levels far beyond the labeled content.

Your lack of testing of the **(b)(4)** increased the potential risk to patients. By not analyzing your components for identity, purity, strength, and quality, you failed to detect a powder blend mixture of substandard quality used in the manufacture of your drug product.

Your response is inadequate because you failed to provide corrective actions to ensure verification of the identity and quality of each component received prior to use in production of drugs.

In response to this letter, provide your plan to test any current and future inventory of the**(b)(4)**.

2. Your firm does not have adequate written procedures for production and process controls designed to assure that the drug products you manufacture have the identity, strength, quality and/or purity they purport or are represented to possess. (21 CFR 211.100(a))

For example, your procedures for manufacturing Infants' Teething Tablets and Infants' Cold Tablets are not supported by adequate process validation. The analytical "standard" used for the Fourier transform infrared spectroscopy (FTIR) identity testing in your process validation study was not a properly qualified standard; it was simply material from your first process validation lot. Your

response is inadequate because you did not provide a corrective action to address the FTIR testing standard.

Your process validation study, used to support your production and process control procedures, did not identify potential sources of variation, or what parameters should be monitored or controlled, to produce a 2

product of acceptable quality with consistent attributes. Process validation studies lacked data to demonstrate that the process is capable of reproducibly yielding finished drugs that consistently meet label claims. Our investigators collected samples in which FDA detected atropine and scopolamine in belladonna teething tablets at concentrations that demonstrated highly variable levels of active ingredient in finished units. These tablets also contained belladonna content that was much higher than both finished product label claims and the purported content of the **(b)(4)** component.

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.

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

In response to this letter, provide your scientific approach for characterizing and qualifying analytical standards used in process validation activities. Regarding your process validation program, include a data-driven and scientifically sound program that appropriately identifies and controls sources of variability, such that the finished product will consistently meet its quality attributes and label claims.

3. Your firm failed to thoroughly investigate any unexplained discrepancy or failure of a batch or any of its components to meet its specifications, whether or not the batch has already been distributed. (21 CFR 211.192)

For example, your firm's investigation into a serious consumer complaint (seizure) for Infants' Teething Tablets lot 41116 included examination of retains for appearance. While your investigation report states that samples were sent to QC for analysis, there was no documentation of what, if any, additional analysis was performed.

Also, you did not conduct investigations of temperature excursions in the warehouse where **(b)(4)** and finished drug products are stored. Your response is inadequate in that it does not support your assertion that temperature excursions did not compromise the quality of the drug product. You label your product with an expiration date, which indicates that temperature excursions could compromise the quality of the drug products. You are required to investigate any excursions from established storage conditions to determine if drug product quality attributes are compromised.

Lastly, expired **(b)(4)** was used to manufacture finished product lots 41116 and 43436, which were released. However, you did not investigate any impact from the use of the expired components on finished products.

In response to this letter, provide details on remediation of your systems used to conduct thorough investigations into complaints, discrepancies, or failures to meet specifications.

Misbranding Violations

Your firm's product, "Homeopathic Infant's Teething Tablets" is a drug under section 201(g)(1) of the FD&C Act [21 U.S.C. 321(g)(1)], because it is intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease, and/or because it is intended to affect the structure or any function of the body. Examples of claims that establish the intended uses for "Homeopathic Infant's Teething Tablets" include, but may not be limited to, the following:

- "Natural relief of pain & irritability from teething"
- "Temporarily relieves the symptoms of simple restlessness and wakeful irritability due to cutting teeth."
- "Helps reduce gum redness and pain."

Under section 502(a) of the FD&C Act [21 U.S.C. 352(a)], a drug is misbranded if its labeling is false or misleading in any particular. FDA's test results on samples of "Homeopathic Infant's Teething Tablets" indicate alkaloid content that widely varies from the content stated on the product labeling, including alkaloid content that far exceeded the labeled claim of alkaloids for "Homeopathic Infant's Teething Tablets." This product is misbranded under section 502(a) of the FD&C Act because the quantity of belladonna alkaloids listed in the labeling does not accurately reflect the quantity of belladonna alkaloids found in the tablets analyzed by FDA. It is a prohibited act to introduce or deliver for introduction into interstate commerce a misbranded drug under section 301(a) of the FD&C Act [21 U.S.C. 331(a)].

We recognize that "Homeopathic Infant's Teething Tablets" is labeled as a homeopathic drug with active ingredients measured in homeopathic strengths. Under section 201(g)(1) of the FD&C Act [21 U.S.C. 321(g)(1)], the term "drug" includes articles recognized in the official Homeopathic Pharmacopeia of the United States (HPUS), or any supplement to it. Homeopathic drugs are subject to the same regulatory requirements as other drugs; nothing in the Act exempts homeopathic drugs from any of the requirements related to adulteration, labeling, misbranding, or approval. We acknowledge that many homeopathic drugs are manufactured and distributed without FDA approval under enforcement policies set out in the Agency's Compliance Policy Guide entitled, "Conditions Under Which Homeopathic Drugs May be Marketed (CPG 400.400)" (the CPG). As its title suggests, the CPG identifies specific conditions under which homeopathic drugs may ordinarily be marketed; thus, in order to fall under the enforcement policies set forth in the CPG, a homeopathic product must meet the conditions set forth in the CPG.

Recall Initiated and Cessation of Manufacture of Certain Drug Products

We acknowledge that your firm initiated a recall after receiving notice of FDA's laboratory findings indicating belladonna levels greatly exceeding the label claim. We also acknowledge your statement that you no longer manufacture Homeopathic Infants' Teething Tablets, Kid's Ear Relief Liquid, and Diarrhea Relief tablets. In your response, confirm that you have permanently ceased production of these drugs. Or, if you are considering resumption of production in the future, notify us of this intention and the timing of resumption.

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.

Correct the violations cited in this letter promptly. Failure to promptly correct these violations may result in legal action without further notice including, without limitation, seizure and injunction. Unresolved violations in this warning letter may also prevent other Federal agencies from awarding contracts.

Until these violations are corrected, we may withhold approval of pending drug applications listing your facility. We may re-inspect to verify that you have completed your corrective actions. We may also refuse your requests for export certificates.

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 reply to:

Liatte Krueger
Compliance Officer
U.S. Food and Drug Administration
10 Waterview Boulevard, 3rd Floor
Parsippany, New Jersey 07054

If you have any questions about this letter, contact Liatte Krueger at (973) 331-4933. Please identify your response with CMS #516099.

Sincerely,
/s/
Diana Amador-Toro
District Director
New Jersey District
Office of Regulatory Affairs,
U.S. Food and Drug Administration
10 Waterview Boulevard, 3rd Floor
Parsippany, New Jersey 07054