RIJ Pharmaceutical LLC 3/28/19

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

WARNING LETTER
CMS# 558815

March 28, 2019

Mr. Timothy Sawyer
Chief Executive Officer
RIJ Pharmaceutical LLC
40 Commercial Avenue
Middletown, NY 10941-1444

Dear Mr. Sawyer:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, RIJ Pharmaceutical (FEI# 1000120212) at 40 Commercial Avenue, Middletown, New York, from April 3 to 13, 2018.

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).

We reviewed your May 4, 2018, response in detail and acknowledge receipt of your subsequent correspondence.

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

1. Your firm failed to establish adequate written procedures for production and process control designed to assure that the drug products you manufacture have the identity, strength, quality, and purity they purport or are represented to possess, and your firm's quality control unit did not review and approve those procedures, including any changes (21 CFR 211.100(a)).

Water System
You have not shown that your water system can consistently produce water suitable for drug manufacturing, and, at a minimum, meets the USP purified water monograph and appropriate microbial limits. You manufactured oral liquid drugs with water that exceeded microbiological action limits in multiple instances. In addition, upstream points in your water system also had excessive levels of bioburden.

Water systems with a pattern of high microbial counts are indicative of a fundamentally flawed design that permits biofilm formation at one of more points in the system. High upstream bioburden counts within water systems can overwhelm the capability of downstream purification components.

It is essential that you design your water system to ensure consistently high purity water that is suitable for its intended use. High bioburden or objectionable microbes in the water used as an ingredient in your drugs may pose significant risk to consumers.

In your response, you stated that you have improved your water system. You did not address findings of high microbial counts immediately after carbon treatment. You also did not address potentially pathogenic gram-negative bacteria, such as *Neisseria* sp., *Pseudomonas* sp., and *Burkholderia* sp. that were identified downstream in your system, including at points-of-use. You did not provide an adequate ongoing microbial monitoring procedure that routinely tests water to ensure the system remains in a state of control. Weekly monitoring is insufficient given your extensive use of water in manufacturing operations and the indications of the products you produce, which include liquid drugs for children and infants.

In response to this letter, provide the following.

- A comprehensive, independent assessment of your water system design, control, and maintenance.
- A comprehensive corrective action and preventive action (CAPA) plan to fully remediate design, control, and maintenance of your water system. Include detailed blueprints of your redesigned system. List all its components and materials of construction. Describe which parts of the equipment were replaced, and state whether any components were retained from the old system. Also include the summary of improvements made to your program for ongoing control and maintenance.
- Your purified water system validation report, conducted only after design, control, and maintenance improvements are implemented.
- Appropriate total count limits for each stage to ensure this system produces water suitable for the intended uses of each of your products. Note that total count limits tighter than your current limits are appropriate, because your firm manufactures liquid products. Also include your water monitoring SOP, with increased microbial sampling frequencies at points-of-use.

Process Controls
You have not conducted process validation studies for the mixing of your drug products. You manufactured super-potent batches that needed to be reworked or reprocessed due to high variability in your mixing process. For example:

Product	*Active ingredient*	*Cause (per Firm)*	*Corrective Action*
Acetaminophen elixir	**(b)(4)**%	Inadequate mixing time	Added additional mixing time and released
Pseudoephedrine liquid	**(b)(4)**%	Inaccurate measurement method of dispensed water	Added water and released

Your firm manufactures products such as a pediatric acetaminophen elixir that can cause serious adverse effects if significantly super-potent.

In your response, you said you plan to validate the mixing processes for your manufacturing operations. Your response was inadequate because you failed to provide a detailed process performance qualification protocol and a program for ensuring maintenance of a validated process throughout the product lifecycle.

Process validation evaluates the soundness of design and state of control of a process throughout its lifecycle. Each significant stage of a manufacturing process must be designed appropriately and assure the quality of raw material inputs, in-process materials, and finished drugs. Process qualification studies determine whether an initial state of control has been established. Successful process qualification studies are necessary before commercial distribution. Thereafter, ongoing vigilant oversight of process performance and product quality is necessary to ensure you maintain a stable manufacturing operation throughout the product lifecycle.

In response to this letter, provide a validation plan for ensuring a state of control throughout the product lifecycle. Include a timeline for performing appropriate process performance qualification (PPQ) for each of your drug products. Describe your program for monitoring batch-to-batch variation to ensure an ongoing state of control. Also include your process performance protocol(s) and your written procedures for qualification of equipment and facilities.

2. Your firm failed to establish laboratory controls that include scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to assure that components, drug product containers, closures, in-process materials, labeling, and drug products conform to appropriate standards of identity, strength, quality, and purity (21 CFR 211.160(b)).

Your microbiological test methods are not adequately verified or validated. You have not shown that your methods can recover pathogenic microorganisms in your liquid finished products.For example, you lacked adequate testing of your products for *B. cepacia,* which has been recovered in your water system.

You also failed to test all your drugs for impurities specified by the USP drug monographs, and you did not verify (or where applicable, validate) your test methods, such as your finished product elixir acetaminophen potency assay.

In your response, you stated that you would perform method validations for the assays specifically cited on the Form FDA 483. Your response was incomplete because it did not address the need to ensure that all your finished product tests and raw material methods are validated (or verified if compendial).

In response to this letter, provide the following.

- A review of all your drug products covered by a USP monograph to determine whether your tests (including but not limited to impurities testing) conform to monograph requirements.
- A detailed plan for your implementation of appropriate testing for all critical quality attributes.
- A list of all your microbiological and chemical tests performed for each batch of product prior to release.

- A summary of your review of the validation/verification status of your microbiological test methods for purified water, raw materials, and finished product testing.
- A comprehensive, independent review of your laboratory practices, procedures, methods, equipment, and analyst competencies. Based on this review, provide a detailed CAPA plan to remediate your laboratory system. Your plan should include the process you will use to evaluate the effectiveness of your implemented CAPA plan.

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

Your investigations were not thorough and did not fully address non-conforming products on the market. You failed to adequately investigate the stability of your sennosides laxative syrup after complaints about product odors. You determined that the root cause of the atypical odors was a reaction of methylparabens with improperly cured containers. However, the CAPA you implemented were inadequate: you concluded that the product was safe although it may not remain stable over its shelf-life. You failed to recall these products.

In your response, you said that the product owner performed a toxicological study of the defective product and found it did not pose risks. Your response was inadequate. You did not evaluate all product lots for stability in this reactive container-closure system to ensure it would meet all specifications over its shelf-life, including but not limited to assay and impurity profile.

In response to this letter, provide the following:

- Data to show that your packaged sennosides laxative syrup is stable over the intended shelf-life, and an action plan to address any nonconforming products still in distribution, including potential recalls or market withdrawals.
- A comprehensive, independent assessment of your system for investigating deviations, atypical events, complaints, OOS results, and failures. Your CAPA plan should include, but not be limited to, improvements in investigations, root cause analysis, written procedures, and quality unit oversight. Also include your process for evaluating CAPA plan effectiveness.
- A comprehensive, independent review of your material system to determine whether all containers, closures, and ingredients from each supplier are qualified and assigned appropriate expiration or retest dates. The review should also determine whether incoming material controls are adequate to prevent use of unsuitable containers, closures, and components.

4. Your firm failed to establish adequate written responsibilities and procedures applicable to the quality control unit and to follow such written procedures and to follow written procedures applicable to the quality control unit (21 CFR 211.22(d)).

Your firm added **(b)(4)** to your docusate liquid drug product with no quality unit review, stability studies, or updates to your master batch records. Your quality unit must evaluate changes to formulations and document potential quality impact prior to implementation.

In your response, you said you added **(b)(4)** as a **(b)(4)** and that you amended the master batch records for docusate liquid, dioctyl liquid, and syrup. Your response was inadequate. You did not review all drug product master batch records for accuracy, and you did not provide sufficient data to support the changes.

In response to this letter, provide the following:

- A comprehensive, independent evaluation of your change management system. This review should include, but not be limited to, your procedure(s) to ensure changes are justified, reviewed, and approved by your quality unit.

The change management program should also include provisions for determining change efficacy.

- A detailed review of all manufacturing changes implemented without adequate change control and supporting data, including stability data.
- Your annual product review procedure.
- A comprehensive assessment and CAPA to ensure your quality unit is given the authority and resources to effectively function. The assessment should also include, but not be limited to:
  - A determination of whether procedures used by your firm are robust and appropriate.
  - Provisions for quality unit oversight throughout your operations to evaluate adherence to appropriate practices.
  - A complete and final review of each batch and its related information before the quality unit disposition decision.
  - Oversight and approval of investigations and discharging of all other quality unit duties to ensure identity, strength, quality, and purity of all products.

5. Your firm failed to ensure that laboratory records included complete data derived from all tests necessary to assure compliance with established specifications and standards (21 CFR 211.194(a)).

You failed to justify aborted and deleted finished drug HPLC (high performance liquid chromatography) analyses, including but not limited to approximately:

- **(b)(4)** aborted sample sets for assays for diphenhydramine oral liquid
- **(b)(4)** aborted sample sets for pseudoephedrine HCL syrup
- **(b)(4)** aborted sample sets for acetaminophen elixir
- **(b)(4)** deleted sample sets for pseudoephedrine HCL syrup

Your laboratory must retain CGMP data to enable the quality unit to make appropriate assessments and decisions about batch disposition, and to demonstrate ongoing control.

In your response, you said you will record your rationale for aborting runs, and you enabled your software to include comments in your HPLC electronic files. Your response was inadequate. You did not provide a revised SOP with clear instructions on the limited instances in which it may be acceptable to abort a run, and how to fully investigate and document such instances.

Your quality system does not adequately ensure the accuracy and integrity of data to support the safety, effectiveness, and quality of the drugs you manufacture. See FDA's guidance document *Data Integrity and Compliance With Drug CGMP* for guidance on establishing and following CGMP compliant data integrity practices at https://www.fda.gov/downloads/drugs/guidances/ucm495891.pdf.

We strongly recommend that you retain a qualified consultant to assist in your remediation.

In response to this letter, provide the following:

- A comprehensive investigation into the extent of the inaccuracies in data records and reporting including results of the data review for drugs distributed to the United States. Include a detailed description of the scope and root causes of your data integrity lapses.
- A current risk assessment of the potential effects of the observed failures on the quality of your drugs. Your assessment should include analyses of the risks to patients caused by the release of drugs affected by a lapse

of data integrity and analyses of the risks posed by ongoing operations.

- A management strategy for your firm that includes the details of your global corrective action and preventive action plan. The detailed action plan should describe how you intend to ensure the reliability and completeness of all data generated by your firm including microbiological and analytical data, manufacturing records, and all data submitted to FDA.

Quality Unit Authority
Significant findings in this letter indicate that your quality unit is not able to fully exercise its authority and/or responsibilities. You must provide the quality unit with appropriate authority, sufficient resources, and staff to carry out its responsibilities to consistently ensure drug quality.

CGMP Consultant Recommended
Based upon the nature of the violations deviations we identified at your firm, we strongly recommend engaging a consultant qualified as set forth in 21 CFR 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 resolving all deficiencies and systemic flaws to ensure ongoing CGMP compliance.

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 in all your facilities.

If you are considering an action that is likely to lead to a disruption in the supply of drugs produced at your facility, FDA requests that you contact CDER's Drug Shortages Staff immediately, at drugshortages@fda.hhs.gov, so that FDA can work with you on the most effective way to bring your operations into compliance with the law. Contacting the Drug Shortages Staff also allows you to meet any obligations you may have to report discontinuances or interruptions in your drug manufacture under 21 U.S.C. 356C(b) and allows FDA to consider, as soon as possible, what actions, if any, may be needed to avoid shortages and protect the health of patients who depend on your products.

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.

Please send your electronic response to Please identify your response with FEI# 1000120212. **orapharm1_responses@fda.hhs.gov (mailto:orapharm1_responses@fda.hhs.gov)**. Please reach out to Compliance Officer, Yvette Johnson, at **yvette.johnson@fda.hhs.gov (/ICECI/EnforcementActions/WarningLetters/default.htm)** with any questions.

Sincerely,
/S/

Diana Amador-Toro
Division Director /OPQO Division I
New Jersey District Office

More in Warning Letters (/ICECI/EnforcementActions/WarningLetters/default.htm)