Andapharm, LLC 2/28/19

U.S. FOOD & DRUG ADMINISTRATION

Office of Pharmaceutical Quality Operations, Division 2
4040 North Central Expressway, Suite 300
Dallas, Texas 75204-3158

February 28, 2019

Case # 566492

WARNING LETTER

VIA UPS EXPRESS

Fedner Destine, President and General Manager
ANDAPharm, LLC
5315 N.W. 35th Terrace
Fort Lauderdale, Florida 33309

Mr. Destine:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, ANDAPharm, LLC at 5315 N.W. 35th Terrace, Fort Lauderdale, Florida, from July 10 to 18, 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 August 3, 2018, response in detail.

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

1. Your firm failed to establish and follow adequate written procedures for cleaning and maintenance of equipment (21 CFR 211.67(b)).

You are a contract manufacturer who makes several products for multiple customers. Your cleaning and maintenance program is inadequate. For example, deficiencies in your program included extended hold times for dirty equipment, such as your encapsulator, that were unsupported by validation data. In addition, you did not establish timeframes for replacing parts and cleaning your tablet coating equipment.

Your management stated you have not cleaned this equipment’s exhaust system since its installation in 2007.

It is important that you demonstrate that your cleaning and maintenance procedures are adequate to prevent product cross-contamination.

In your response, you stated that you will develop a cleaning validation plan, train your employees, and develop a “system of daily quality assurance walkthroughs.” Your response is inadequate because you did not provide details of your cleaning validation plan.

This is a repeat violation from your 2012 and 2016 inspections. In response to this letter, provide:

- Clarification on what your “daily quality assurance walkthroughs” entail.
- A comprehensive plan to evaluate the adequacy of cleaning procedures, practices, and validation studies for each piece of manufacturing equipment used to manufacture more than one product. Include a summary of standard operating procedure (SOP) updates that will establish an appropriate program for validation of cleaning procedures for new products, processes, and equipment. Also describe your ongoing verification program to ensure cleaning procedures continue to be effective.
- Scientific rationale for your cleaning validation strategy. Describe updates to your cleaning validation protocol to incorporate worst case conditions. These should include but not be limited to:
    - Evaluating drugs of the highest toxicity;
    - Assessing drugs of the lowest solubility in their cleaning solvents;
    - Evaluating drugs with characteristics that make them difficult to clean; and,
    - Swabbing equipment locations that are most difficult to clean.
- A plan for determining the identity and reducing the amount of accumulated product residue in your manufacturing rooms.

2. Your firm failed to establish and follow an adequate written testing program designed to assess the stability characteristics of drug products (21 CFR 211.166(a)).

Your stability protocols for multiple lots of hyoscyamine sulfate, salsalate, and phenazopyridine drug products lacked information pertaining to the tests, storage conditions, and length of study. Also, your stability summary reports for multiple lots of these products were missing data for certain time points. Reliable stability data is critical for ensuring that products maintain their identity, strength, quality, purity, and safety throughout their shelf-lives.

In your response, you provided a copy of your blank stability protocol template that highlights the headings of sections that our investigator noted as missing. However, your response is inadequate because you did not address the missing data or attempt to clarify under what conditions stability samples were handled in the past (e.g., tests, storage conditions, and length of study). Also, you did not address the missing time points in your stability summary reports.

This is a repeat violation from your 2012 and 2016 inspections. In response to this letter, provide:

- A summary of all accelerated and long-term stability data that support the expiration dates for your drug products, including annotation of any out-of-specification results obtained during testing (regardless of whether they were later invalidated).
- Your assessment of the impact of the missing stability data on product quality.
- A comprehensive, independent assessment and corrective actions and preventive actions (CAPA) to ensure the adequacy of your stability program. Your CAPA should include, but not be limited to:
    - A remediated SOP describing your stability program;
    - Stability-indicating methods;
    - Stability studies to support each drug product in its container-closure system before distribution is permitted;
    - An ongoing program in which representative batches of each product are added each year to the program to determine if the shelf-life claim remains valid; and,
    - Specific attributes to be tested at each station.

3. Your firm failed to have separate or defined areas or such other control systems necessary to prevent contamination or mix-ups (21 CFR 211.42(c)).

We observed rejected lots of phenazopyridine, salsalate, chloradiazepoxide/clindium bromide in your receiving area. These lots were not labeled as “rejected” nor were they recorded as “rejected” in the Reject Log Book. As a contract manufacturer, it is important that you maintain adequate control over your material flow and segregation to avoid potential mix-ups and release of rejected lots.

We also observed two open boxes of in-process salsalate tablets lot M810F18-1 in the “ante room” between Manufacturing Rooms **(b)(4)** and **(b)(4)**. The “ante room” is not monitored for temperature and humidity. Its doors also had various breaches.

In your response, you stated that you scheduled third-party disposal of the rejected drugs in your receiving area and trained your employees on documentation of rejected materials. This response is inadequate because it is unclear what your procedures entail and how you will monitor compliance with the procedures.

Your response also stated that the salsalate tablets “were not supposed to be opened in the ante room.” You stated your “ante room” did not have temperature monitoring, but was part of the facility heating, ventilation, and air-conditioning system. You also stated that the salsalate tablets were “manufactured under CGMP conditions” and were tested to meet specifications. The response did not adequately address whether exposure to unknown temperatures and humidity affected the stability of the lot. Furthermore, inappropriate bulk staging of the salsalate tablets indicates they were not “manufactured under CGMP conditions.” In addition, you cannot solely rely on release testing to ensure that you have met CGMP conditions. Products must be manufactured under an ongoing state of CGMP control.

In response to this letter, provide a risk assessment on all lots of your drug products that may have been exposed to environmental conditions that were potentially processed or held outside of appropriate storage specifications, including stability data on salsalate tablet lot M810F18-1. Also provide the status of your facility repair work as well as a summary of your procedures on material segregation, flow, and disposal.

4. Your firm failed to follow 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 to document at the time of performance (21 CFR 211.100(b)).

Some manufacturing data was recorded on secondary, uncontrolled notebooks or on loose sheets of scratch paper. We observed an uncontrolled notebook in Manufacturing Room **(b)(4)** that contained tares, raw material release labels, and remaining amounts of raw materials. We also observed a slip of loose paper with production information. Complete, consistent, and accurate data should be attributable, legible, contemporaneously recorded, original or a true copy, and accurate.

In your response, you stated that you will not allow the use of secondary notebooks or loose pieces of paper in the process rooms and indicated that you issued an internal memo informing all employees that failure to properly document processes at time of performance will result in automatic dismissal. Your response is inadequate because it does not include a detailed and comprehensive strategy to ensure records are completed and maintained in accord with CGMP (e.g., including CGMP documentation checks in your proposed system of daily quality assurance reviews).

In response to this letter, provide a complete assessment of documentation systems used throughout your manufacturing and laboratory operations to determine where documentation practices are insufficient. Include a detailed CAPA plan that remedies documentation practices and ensures you retain complete and accurate records.

Quality systems guidance

Your firm’s quality systems are inadequate. For guidance on establishing and following CGMP compliant quality systems, see FDA’s guidances: *Q8(R2) Pharmaceutical Development* at **https://www.fda.gov/downloads/drugs/guidances/ucm073507.pdf; *Q9 Quality Risk Management* at (https://www.fda.gov/downloads/drugs/guidances/ucm073507.pdf)https://www.fda.gov/downloads/Drugs/Guidances/ucm073511.pdf; and *Q10 Pharmaceutical Quality System* at (https://www.fda.gov/downloads/Drugs/Guidances/ucm073511.pdf)https://www.fda.gov/downloads/drugs/guidances/ucm073517.pdf. (https://www.fda.gov/downloads/drugs/guidances/ucm073517.pdf)**

Responsibilities as a contractor

Drugs must be manufactured in conformance with CGMP. FDA is aware that many drug manufacturers use independent contractors, such as production facilities, testing laboratories, packagers, and labelers. FDA regards contractors as extensions of the manufacturer.

You are responsible for the quality of drugs you produce as a contract facility, regardless of agreements in place with product owners. You are required to ensure that drugs are made in accordance with section 501(a)(2)(B) of the FD&C Act for safety, identity, strength, quality, and purity. See FDA’s guidance document *Contract Manufacturing Arrangements for Drugs: Quality Agreements* at **https://www.fda.gov/downloads/drugs/guidances/ucm353925.pdf. (https://www.fda.gov/downloads/drugs/guidances/ucm353925.pdf)**

CGMP consultant recommended

Because you failed to correct repeat violations, 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 fully 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.

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.

Your written notification should refer to the Warning Letter Number above,Case #. 566492 Please electronically submit your signed reply on your firm's letterhead to CDR John W. Diehl, M.S., Director, Compliance Branch, **at john.diehl@fda.hhs.govand (mailto:john.diehl@fda.hhs.gov)orapharm2_responses@fda.hhs.gov. (mailto:orapharm2_responses@fda.hhs.gov)**

If you have questions regarding the contents of this letter, please contact Ms. Rebecca Asente, M.S., Compliance Officer, at (504) 846-6104 or **Rebecca.asente@fda.hhs.gov. (mailto:Rebecca.asente@fda.hhs.gov)**

Sincerely,
/S/
Monica R. Maxwell
Program Division Director
Office of Pharmaceutical Quality Operations,
Division II

CC:
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Division of Drugs, Devices and Cosmetics
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