WARNING LETTER

Allay Pharmaceuticals, LLC

MARCS-CMS 609023 — JANUARY 27, 2021

Delivery Method:

VIA Electronic Mail

Product:

Drugs

Recipient:

Rosy Sultana

CEO & President

Allay Pharmaceuticals, LLC

16600 NW 54th Ave, Unit 23
Hialeah, FL 33014-6109
United States

Issuing Office:

Division of Pharmaceutical Quality Operations II

United States

January 27, 2021

Case # 609023

Warning Letter

Ms. Sultana:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Allay Pharmaceuticals, LLC, FEI 3007007565, at 16600 NW 54th Avenue, Unit 23, Hialeah, Florida, from May 5 to 15, 2020.

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

Additionally, your **(b)(4)** tablets are adulterated under section 501(b) of the FD&C Act, 21 U.S.C. 351(b) for failure to conform to compendial standards for strength, quality, or purity.

Information and records gathered during the course of the inspection reflect that your products are intended to treat a disease or condition. Therefore, your products, **(b)(4)**, are drugs as defined in section 201(g) of the FD&C Act [21 U.S.C. 321(g)]. Your products, which contain **(b)(4)** are also biological products as defined in section 351(i)(1) of the Public Health Service Act (PHS Act) [42 U.S.C. 262(i)(1)] because they are a "protein" as defined in 21 C.F.R. 600.3(h)(6), or are "analogous" to a protein because the identified biological product (i.e., protein) component in these naturally derived mixtures is necessary for the activity of the product and contributes to achieving the intended therapeutic effect.

We reviewed your June 6, 2020, response to our Form FDA 483 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 (21 CFR 211.100(a)).

Your firm failed to adequately validate the manufacturing processes for your **(b)(4)** tablets. You lacked adequate data to show homogeneity of your drug product during manufacturing . During your process performance qualification (PPQ), blend samples were **(b)(4)** before analysis. When samples are **(b)(4)**, it potentially masks the variability of your blend. In addition, you obtained an out-of-specification (OOS) assay result for one of the active ingredients, **(b)(4)**, in your post-compression testing of **(b)(4)** strength PPQ lot **(b)(4)**.

FDA also collected three samples of **(b)(4)** tablets during the inspection, two of which were from your process validation lots. All three samples were sub-potent for the active ingredient, **(b)(4)**. One of the three also failed content uniformity for **(b)(4)**.

Appropriate controls and understanding of your manufacturing process is essential to ensuring a safe and effective drug product. We acknowledge that your firm has agreed to voluntarily recall lots **(b)(4)** and **(b)(4)**, and to voluntarily destroy lot **(b)(4)** which you indicated was not distributed to the market.

The blend process is a critical step in the manufacture of oral solid dosage forms, particularly for **(b)(4)**. Inadequate handling of blends can promote segregation, increase moisture levels, cause aggregation of particles, and lead to inconsistent flow characteristics. Additionally, because of the **(b)(4)** range of this product, content uniformity is critical; it is especially important to prevent patients with **(b)(4)** from receiving insufficient or excessive doses.

In your response, you indicated that you will perform concurrent validation to collect sufficient data to evaluate product behavior. Your deviation investigation into the OOS result was in progress and you have developed a revised validation protocol.

Your response is inadequate because you have not provided sufficient data to show where variability is occurring in your process and how you will control it before re-performing validation. In addition, you did not provide a copy of your revised validation protocol. Your use of a concurrent validation approach is inappropriate as you do not appear to have a high degree of understanding of the sources of variation in your manufacturing processes. Furthermore, concurrent validation should be rarely used.

Your manufacturing failures indicate that you do not have an adequate ongoing program for monitoring process control to ensure stable manufacturing operations and consistent drug quality. See FDA's guidance document Process Validation: General Principles and Practices for general principles and approaches that FDA considers to be appropriate elements of process validation at https://www.fda.gov/downloads/drugs/guidances/ucm070336.pdf (https://www.fda.gov/downloads/drugs/guidances/ucm070336.pdf).

In response to this letter, provide the following:

• A data-driven and scientifically sound analysis that identifies all sources of variability including, but not limited to, raw materials and manual steps (e.g., hand scooping). Determine the capability of each manufacturing process step and provide your corrective action and preventive action (CAPA) plan to reduce process variation.

• A detailed summary of your validation program for ensuring a state of control throughout the product lifecycle, along with associated procedures. Describe your program for process performance qualification, and ongoing monitoring of both intra-batch and inter-batch variation to ensure a continuing state of control.

• A timeline for performing appropriate process performance qualification (PPQ) for each of your **(b)(4)** tablet drug products.

• Include your process performance protocol(s), and written procedures for qualification of equipment and facilities.

2. 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 firm failed to perform a thorough investigation after being informed that FDA testing found OOS assay results for one lot of **(b)(4)** tablets.

You manufacture **(b)(4)** tablets under contract for the product owner, **(b)(4)**. In the quality agreement with the product owner, you have the primary responsibility for investigating OOS results.

The active ingredient assay specifications you developed with the product owner for **(b)(4)** and **(b)(4)** in your **(b)(4)** products were not appropriate. On April 14, 2020, you were informed of the sub-potent test results and inadequate specification. The active ingredient assay specifications you established with your product owner for **(b)(4)** and **(b)(4)** were **(b)(4)**%. However, the United States Pharmacopeia (USP) monograph for **(b)(4)**, USP has **(b)(4)** and **(b)(4)** assay acceptance criteria of **(b)(4)**%.

(b)(4) outside of the USP acceptance criteria are adulterated within the meaning of section 501(b) of the FD&C Act, 21 U.S.C. 351(b), in that their strength, quality, or purity falls below the standards set forth in an official compendium recognized in the FD&C Act. FDA notified your customer of this violation in Warning Letter **(b)(4)**.

Articles represented as a drug recognized in an official compendia must conform to the compendial standards for strength, quality, or purity. We acknowledge that you updated the **(b)(4)** tablets active ingredient assay specification.

Your investigation into the OOS sample result was inadequate and did not identify CAPA. Furthermore, an investigation was not performed to ensure that previously released lots met your revised assay specifications. FDA investigators found 13 lots within expiry that exceeded your new assay specification during release or stability testing. These lots should have been identified in your investigation.

In your response, you stated that you reviewed the batch records and analytical records.

Your response is inadequate as you are responsible for conducting a thorough investigation when you become aware that your product may not in compliance with CGMP.

In response to this letter, provide the following:

• A review of all other products you manufacture to determine whether or not their specifications are appropriate and justifiable. Conduct a risk assessment for any products and corresponding lots lacking appropriate and justifiable specifications. If any products are found to be outside of compendial standards or other appropriate specifications, indicate the corrective actions you will take, including notifying customers and initiating recalls.

• Updated procedures to ensure that product specifications undergo a routine review to ensure they remain appropriate.

• A comprehensive, independent assessment of your overall system for investigating deviations, discrepancies, complaints, OOS results, and failures. Provide a detailed action plan to remediate this system. Your action plan should include, but not be limited to, significant improvements in investigation competencies, scope determination, root cause evaluation, CAPA effectiveness, quality unit oversight, and written procedures. Address how your firm will ensure all phases of investigations are appropriately conducted.

• An action plan with timelines and a summary of results from retain sample testing of all **(b)(4)** tablet lots within expiry. You should test all appropriate quality attributes including, but not limited to, identity and strength of active ingredients of each lot. If testing yields an OOS result, indicate the corrective actions you will take, including notifying customers and initiating recalls.

3. Your firm failed to establish and follow an adequate written testing program designed to assess the stability characteristics of drug products and to use results of stability testing to determine appropriate storage conditions and expiration dates (21 CFR 211.166(a)).

Your stability program is inadequate. You failed to have adequate long-term stability data to support the commercial size validation batches manufactured using API from a new supplier. Also, you failed to follow your stability test protocol by not consistently performing disintegration testing. The validation batches using the new API supplier were manufactured from May 16 to June 25, 2019, but not placed into a long-term stability study until May 1, 2020, almost a year later.

Stability data is critical for ensuring that products maintain their identity, strength, quality, purity, and safety throughout their labeled shelf-lives.

In your response, you indicated that you initiated a deviation investigation for the lack of stability testing and that these deficiencies will not reoccur. A stability coordinator will also be hired to oversee the stability program.

Your response is inadequate because you did not provide interim measures to address the products in the market that are lacking long term stability data.

In response to this letter, provide the following:

• A comprehensive, independent assessment and CAPA plan to ensure the adequacy of your stability program. Your remediated program should include, but not be limited to:
o Stability indicating methods
o Stability studies for each drug product in its marketed container-closure system before distribution is permitted
o 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
o Detailed definition of the specific attributes to be tested at each station (timepoint)

• All procedures that describe these and other elements of your remediated stability program.

4. Your firm's quality control unit failed to exercise its responsibility to ensure drug products manufactured are in compliance with CGMP, and meet established specifications for identity, strength, quality, and purity (21 CFR 211.22).

Your quality unit (QU) failed to adequately oversee the quality of components received from your supplier and your drug manufacturing operations. For example:

• The variability in API assay results reported by your supplier compared to your testing was not adequately evaluated. The variability observed may compromise the assay and content uniformity of your finished product. For example, your firm's test results for API lot **(b)(4)**, used in the manufacture of **(b)(4)** tablets **(b)(4)** lot **(b)(4)**, had a difference of 7.8% from the API manufacturer's certificate of analysis (COA). Your firm used your assay result to formulate the finished product. Additionally, the FDA sampled lot **(b)(4)** and the sample results failed to meet the USP assay specification for active ingredient, **(b)(4)**, and for content uniformity. In your communication dated September 15, 2020, your firm indicated that this lot was not distributed and will be destroyed.

Per the quality agreement with **(b)(4)**, your firm is responsible for the qualification of approved manufacturers. However, during the inspection you had not qualified the new API supplier and you relied on **(b)(4)** to perform qualification of the supplier, which is contrary to the agreement.

• Computerized systems in the laboratory had inadequate controls.

• Complaints were not adequately reviewed and investigated.

In your response you stated that your firm recognizes the need to have more interactions with the API manufacturer. You committed to investigating and communicating to the API manufacturer when API release testing results differ more than 3%. Additionally, you have contacted the manufacturer of your HPLC systems to purchase and validate the necessary equipment. You also indicated that your new complaint procedure includes tracking, trending, and evaluating complaints.

Your response is inadequate. You did not describe when and how you will requalify your API supplier or provide justification for how you determined when differences in API assay need to be investigated. In addition, you did not perform a retrospective review of the test results for your previous API supplier, **(b)(4)**. Also, you did not perform an assessment to determine the risk from failing to have audit trail enabled controls and unique user passwords.

See FDA's guidance document *Quality Systems Approach to Pharmaceutical CGMP Regulations* for help implementing quality systems and risk management approaches to meet the requirements of CGMP regulations 21 CFR, parts 210 and 211 at https://www.fda.gov/downloads/Drugs/Guidances/UCM070337.pdf (https://www.fda.gov/downloads/Drugs/Guidances/UCM070337.pdf).

In response to this letter, provide the following:

• A comprehensive independent review of your material system to determine whether all suppliers of components, containers, and closures are each qualified, and the materials are assigned appropriate expiration or retest dates. The review should also determine whether incoming material controls are adequate to prevent use of unsuitable components, containers, and closures.

• The chemical and microbiological quality control specifications you use to test and release each incoming lot of component for use in manufacturing. Include chemical and microbial test methods used to analyze each of your API, along with the corresponding validation or verification if USP methods are used.

• A description of how you will test each component lot for conformity with all appropriate specifications for identity, strength, quality, and purity. If you intend to accept any results from your supplier's COA instead of testing each component lot for strength, quality, and purity, specify how you will robustly establish the reliability of your supplier's results through initial validation as well as periodic re-validation. In addition, include a commitment to always conduct at least one specific identity test for each incoming component lot.

• A summary of results obtained from testing all components to evaluate the reliability of COA from each component manufacturer. Include your SOP that describes this COA validation program.

• A comprehensive assessment and remediation plan to ensure your QU is given the authority and resources to effectively function. The assessment should also include, but not be limited to:
o A determination of whether procedures used by your firm are robust and appropriate.
o Provisions for QU oversight throughout your operations to evaluate adherence to appropriate practices.
o A complete and final review of each batch and its related information before the QU disposition decision.
o Oversight and approval of investigations and discharging of all other QU duties to ensure identity, strength, quality, and purity of all products.
o Also describe how top management supports quality assurance and reliable operations, including but not limited to timely provision of resources to proactively address emerging manufacturing/quality issues and to assure a continuing state of control.

• A detailed description of how your firm will implement an effective system to ensure retention and review of written and electronic laboratory data. Include the following:
o Summarize your interim controls to prevent deletion and modification of data.
o Define the roles and responsibilities of personnel who have access to analytical instruments and data.
o Establish a procedure to ensure that all analytical data including but not limited to sample and standard preparation are documented in accordance with CGMP requirements.

o Detail the user privileges for all staff for each of your analytical systems.
o Provide a detailed summary of your procedural updates and associated training for user role assignments and controls.

Unapproved New Drugs

Based on the information your firm submitted to FDA's electronic Drug Registration and Listing System and the information collected during the May 2020 inspection, FDA has determined that your firm is distributing **(b)(4)** tablets, a biological product, without FDA approval or a valid biologics license.

We encourage you to contact FDA's unapproved drugs coordinator, Dr. Sally Loewke, at 301-796-0710 for assistance in communicating with the FDA on the application process for your unapproved biological product.

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 and your customer **(b)(4)**. have a quality agreement regarding the manufacture of **(b)(4)**. 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/media/86193/download.

CGMP Consultant Recommended

Based upon the nature of the violations 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

The violations cited in this letter are not intended to be an all-inclusive list of violations that exist at your facility. You are responsible for investigating and determining the causes of these violations and for preventing their recurrence or the occurrence of other violations.

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). This also 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.

FDA may also withhold approval of requests for export certificates and approval of pending new drug applications or supplements listing your facility as a supplier or manufacturer until the above violations are corrected. We may re-inspect to verify that you have completed your corrective actions.

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.

If you believe that your products are not in violation of the FD&C Act (or you have complied with FDA regulations), include your reasoning and any supporting information for our consideration.

Please identify your response with FEI 3007007565. Send your electronic reply to Dr. Shawn Larson – Compliance Officer at Shawn.Larson@fda.hhs.gov and ORAPHARM2_Responses@fda.hhs.gov.

If you have questions regarding the contents of this letter, please contact Dr. Larson at 214-253-5216.

Sincerely,
/S/

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

CC: (Redacted Copy)

(b)(4)

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