WARNING LETTER

DuPont Nutrition USA Inc.

MARCS-CMS 627211 — DECEMBER 02, 2022

Delivery Method:

Via Email

Product:

Drugs

Recipient:

Mr. Matthew Davidson

Plant Manager

DuPont Nutrition USA Inc.

1301 Ogletown Rd Newark, DE 19711
United States

Issuing Office:

Division of Pharmaceutical Quality Operations I

United States

Warning Letter #627211

December 2, 2022

Dear Mr. Matthew Davidson:

The U.S. Food and Drug Administration (FDA) inspected your drug excipient manufacturing facility, DuPont Nutrition USA Inc., FEI 3013947845, at 1301 Ogletown Rd, Newark, Delaware, from November 17 to December 15, 2021.

This warning letter summarizes significant deviations from current good manufacturing practice (CGMP) for the manufacture of your excipient, Avicel, which is extensively used as a major component in a wide variety of drug products.

Because your methods, facilities, or controls for manufacturing, processing, packing, or holding do not conform to CGMP, your excipient is 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 excipient is 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.

We reviewed your January 12, 2022, response to our Form FDA 483 in detail and acknowledge receipt of your subsequent correspondence.

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

1. Your firm failed to perform adequate investigation of complaints.

Your firm manufactures microcrystalline cellulose (MCC) under the brand name Avicel, which is included in Drug Master File (DMF) 449 submitted to FDA. Avicel is used as a compression and flow aid in multiple drug product formulations.

Between April 2020 and June 2021, you received approximately 50 complaints related to your Avicel excipient failing to meet the conductivity specifications. The conductivity quality standard for MCC is delineated in the U.S. Pharmacopeia (USP). Failure to meet applicable USP standards also renders drugs adulterated under section 501(b) of the FD&C Act.

You did not adequately evaluate these complaints. You only included retest and release data review in your initial investigation into conductivity complaints for Avicel. It was not until seven months later that you discovered your conductivity meter probe was encrusted with residue, thus giving inaccurate conductivity results. This conductivity meter was used for batch release testing and retesting as part of your complaint investigations. Your initial complaint investigation did not adequately evaluate whether your malfunctioning conductivity probe was potentially associated with these out of specification (OOS) conductivity complaints, especially when you determined that the complaints could not be verified.

Notably, you later linked this fouled conductivity meter to OOS Avicel that you previously released and shipped to your customers. You did not communicate the OOS results to your customers in a timely manner. It took you more than three months after you opened your investigation to initiate communication with your customers. Appropriate action was not initiated against the affected batches until nine months after you became aware of the conductivity test failure.

In your response you state, “product quality customer complaint data for the past 24 months were reviewed for trends that might indicate ineffective investigations or corrective and preventive actions,” and that “there were no significant trends observed.” This is contradictory to the customer complaint records FDA collected during the inspection. Additionally, you did not provide sufficient evidence of your review, including a protocol, the type of complaints reviewed, how many were related to compendial test results, and your evaluation report. You also did not provide details on how you incorporated the numerous Avicel conductivity complaints you received into your review.

In response to this letter, provide 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, corrective action and preventive action (CAPA) effectiveness, quality unit oversight, and written procedures. Address how your firm will ensure all phases of investigations are appropriately conducted.

2. You failed to thoroughly investigate OOS results in a timely manner, appropriately identify root causes, expand investigations to all potentially affected lots, and implement adequate CAPA.

Your investigations into failing test results are inadequate.

You had failing results for conductivity in Avicel lots. Your laboratory OOS results were only investigated by the original analyst using a checklist. The supervisory review did not include an evaluation of the records and test data. You failed to expand the investigation to production and other potentially affected lots. Your investigation also lacked sufficient evidence to determine the root cause and identify CAPAs.

You did not perform a timely and thorough investigation into an inaccurate conductivity meter reading. Your investigation revealed a probe “encrusted with grime/resin” caused lower conductivity values. Although you identified OOS results in November 2020, you did not expand your investigation in a timely manner to determine the scope of potentially impacted lots tested using this meter.

You determined the root cause of the conductivity OOS values was related to elevated levels of ammonium chloride in the Avicel. FDA is concerned as elevated levels of ammonium chloride in excipients has the potential to lead to impurity formation in finished drug products. Of note, such impurity formation could include nitrosamines. For FDA’s current thinking on this topic, see FDA’s guidance, *Control of Nitrosamine Impurities in Human Drugs* at https://www.fda.gov/media/141720/download (https://www.fda.gov/media/141720/download).

In your response you state you conducted a review of laboratory OOS investigations for the past year; however, you did not provide a rationale to support this limited time period versus the standard expiration period of your drugs. In addition, you did not expand this review to manufacturing investigations. Your response also lacks a commitment or details on how to address released excipient associated with process deviations or OOS investigations.

In response to this letter, provide:

- A retrospective, independent review of all invalidated OOS (including in-process and release/stability testing) results for excipients currently in the U.S. market and within expiry as of the date of this letter and a report summarizing the findings of the analysis, including the following for each OOS:

o Determine whether the scientific justification and evidence relating to the invalidated OOS result conclusively or inconclusively demonstrates causative laboratory error.
o For investigations that conclusively establish laboratory root cause, provide the rationale, and ensure that all other laboratory methods vulnerable to the same or similar root cause are identified for remediation.
o For all OOS results found by the retrospective review to have an inconclusive or no root cause identified in the laboratory, include a thorough review of production (e.g., batch

manufacturing records, adequacy of the manufacturing steps, suitability of equipment/facilities, variability of raw materials, process capability, deviation history, complaint history, batch failure history). Provide a summary of potential manufacturing root causes for each investigation, and any manufacturing operation improvements.

- A comprehensive review and remediation plan for your OOS result investigation systems. The CAPA should include, but not be limited to addressing the following:

o Quality unit oversight of laboratory investigations
o Identification of adverse laboratory control trends
o Resolution of causes of laboratory variation
o Initiation of thorough investigations of potential manufacturing causes whenever a laboratory cause cannot be conclusively identified
o Adequately scoping of each investigation and its CAPA
o Revised OOS investigation procedures with these and other remediations

3. Your firm failed to ensure the test methods used are suitable for their intended use.

You are currently using compendial and non-compendial conductivity test methods for in-process and release testing of your Avicel lots. Your firm failed to adequately verify and validate your compendial and non-compendial conductivity methods, respectively. You were unable to provide evidence of method verification and validation prior to April 2021 even though you used these test methods to conduct release testing for Avicel prior April 2021.

A. You failed to verify the compendial conductivity test method and evaluate if additional verification parameters or validation were required due to changes in sample preparation. For example:
o You failed to have an approved method verification protocol with pre-established requirements for your most current (April 13, 2021) test method report. You were also unable to locate the testing instructions for your precision study.
o Your compendial method verification failed to evaluate accuracy of the test method.
o You lacked scientific rationale to support the range evaluated during the method verification (**(b)(4)** of the specification limit).
o You lacked adequate scientific justification to identify an anomalous result obtained during your precision study as an “outlier” and to exclude it from the study.
o Review of your raw data compared to your report indicated discrepancies in the number of samples and the timing of testing.

B. You failed to validate your non-compendial method for in-process and packaging testing.

You attempted to correlate your compendial and non-compendial test methods as part of your validation of your “quick methods.” Your results showed a low correlation and a significant difference between the methods. Of concern, the data showed significantly lower conductivity values when compared to the compendial method. However, you concluded that the methods had good correlation and authorized it for use in production in place of the compendial method. This may have resulted in inaccurately low conductivity results being used to release Avicel that in fact failed USP conductivity requirements.

C. You inappropriately used composite sampling.

While you utilized your non-compendial "**(b)(4)**" for individual packaged samples, the certificate of analysis included the result of the composite sample. A review of the data indicated passing composite sample results comprised of samples which included individual failing packaging samples. The use of composite sampling may have allowed the release of OOS Avicel to the market. Additionally, your practice of composite sampling is concerning considering your non-compendial "**(b)(4)**" provided inaccurate results and you were using composite samples inappropriately for release testing. You lacked an adequate scientific rationale for the use of compendial test methods for composite samples and non-compendial test methods for in-process and packaged samples.

Your response is inadequate. You reiterate that you verified your compendial method but failed to provide adequate information to support this. We acknowledge your commitment to validate your non-compendial test methods, including conductivity and pH.

In response to this letter, provide:

- A comprehensive assessment of test methods used for excipients for drug use to determine their suitability (i.e., compendial method verification, or non-compendial method validation). If verification or validation is needed, provide the corresponding protocols and reports or a plan and timeline for completion of the appropriate activity.
- Improved procedures regarding validation/verification requirements and updated analytical methods.
- A retrospective review of results obtained using unverified/unvalidated compendial and non-compendial methods.
- A summary of the impact assessment for released lots.
- A comprehensive, independent review of your laboratory practices, methods, equipment, and analyst competencies. Based on this review, provide a detailed CAPA plan to fully remediate your laboratory system.
- Your scientific rationale for the use of the compendial test methods for composite samples and non-compendial test methods for in-process and packaged samples.

4. Your firm failed to have an adequate change management program to evaluate and approve changes that may impact the quality of the excipient.

Your Avicel process performance qualification studies conducted from 2001 through 2007 identified conductivity as a critical quality parameter. However, in approximately 2011 you removed the **(b)(4)** conductivity meters without a documented change control.

In your response you state that at the time of the change you evaluated the potential impact on the quality of Avicel but did not document this evaluation. You also state you will evaluate the impact of any other process changes implemented without adequate review on the quality of your excipient. You commit to evaluate process changes for potential impact on other critical

quality parameters listed in your most current validations (dated 2001, 2004, and 2007). However, you did not provide a detailed plan or timeline for implementation of your revised change management program.

In response to this letter, provide:

- A comprehensive, independent assessment of your change management system. This assessment should include, but not be limited to, your procedure(s) to ensure changes are justified, reviewed, and approved by your quality unit. Your change management program should also include provisions for determining change effectiveness.
- A remediation plan that better assures ongoing management oversight throughout the manufacturing lifecycle of all excipients. Provide a more data-driven and scientifically sound program that identifies sources of process variability and assures that manufacturing (including both production and packaging) operations meet appropriate parameters and quality standards. This includes, but is not limited to, evaluating suitability of equipment for its intended use, ensuring quality of input materials, determining the capability and reliability of each manufacturing process step and its controls, and vigilant ongoing monitoring of process performance and product quality.

5. Your firm failed to have adequate laboratory control records that include complete and accurate data from tests performed to ensure conformance with specifications and standards, nor did you record activities at the time of performance.

During the inspection, your laboratory personnel backdated the approval section of an in-house microbiological media preparation worksheet after the media had been used. In addition, your microbiology laboratory personnel were observed using unreleased microbiological growth media plates during drug testing.

Your personnel improperly retested pH, conductivity, loss on drying, and particle size samples. We observed failing results changed to passing based on retest results. You were unable to provide adequate investigations or justification associated with the retests.

Your sample testing records are incomplete because they do not include information about sample weight, and a reference to reagents and instruments used.

Without complete, timely, and accurate testing records, you cannot adequately evaluate the quality of your excipient, make appropriate batch release decisions, or fully understand the potential impact of poor manufacturing practices on the quality of your excipient.

Your response is inadequate. For example:

- You acknowledge the testing record was backdated. However, your investigation lacked a comprehensive assessment into the extent of the data integrity breach. You did not investigate to determine if similar events occurred elsewhere in your facility.
- You state that no other incidents were found for the usage of unapproved media in the microbiology laboratory. You did not provide supporting evidence of this review, and you did not describe the time period of your evaluation. It is not clear whether you expanded your evaluation to the analytical laboratory.

- You commit to establish and validate automatic data transfer to **(b)(4)**, and you acknowledge that not all instruments will be able to transfer data. However, you did not provide a CAPA plan with interim controls to prevent data and file deletion or modification until your **(b)(4)** is updated or how you will manage instruments that cannot transfer data.
- You did not provide an investigation or documented evaluation into changes in results without justification and their impact on distributed excipient.
- You state sample weights for sample preparation were documented on paper for the compendial method. You did not provide supporting evidence.

In response to this letter, provide:

- A comprehensive, independent assessment of your laboratory practices, procedures, methods, equipment, documentation, and analyst competencies. Based on this review, provide a detailed plan to remediate and evaluate the effectiveness of your laboratory system, including specific measures you are taking to ensure all laboratory data is contemporaneously recorded and errors are immediately documented and properly investigated.
- 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 comprehensively remediates your firm's documentation practices to ensure you retain attributable, legible, complete, original, accurate, contemporaneous records throughout your operation.

Data Integrity Remediation

Your quality system does not adequately ensure the accuracy and integrity of data to support the safety, effectiveness, and quality of the excipient you manufacture. You may find principles outlined in the FDA's data integrity guidance helpful as you consider remediating this issue, see *Data Integrity and Compliance With Drug CGMP* at https://www.fda.gov/media/119267/download (https://www.fda.gov/media/119267/download).

We strongly recommend that you hire a qualified third-party auditor/consultant with experience in detecting data integrity problems to assist you with coming into compliance with CGMP requirements. 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 excipient distributed in 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 excipient. Your assessment should include analyses of the risks to patients caused by the release of excipient 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 corrective 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.

Test Results Out-of-Specification

You may find principles outlined in the FDA's OOS guidance helpful as you consider remediating this issue, see *Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production* at https://www.fda.gov/media/71001/download (https://www.fda.gov/media/71001/download).

A possible laboratory error is insufficient to close an investigation. Whenever an investigation lacks conclusive evidence of laboratory error, a thorough investigation of potential manufacturing causes should be performed.

CGMP Consultant Recommended

Based upon the nature of the deviations we identified at your firm, we strongly recommend engaging a consultant qualified to evaluate your operations and to assist your firm in meeting excipient CGMP requirements. We also recommend that the qualified consultant perform a comprehensive audit of your entire operation for CGMP compliance and that the consultant evaluate the completion and efficacy of your corrective actions and preventive actions before you pursue resolution of your firm's compliance status with FDA.

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

If you are considering an action that is likely to lead to a disruption in the supply of drug 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 any deviations promptly. Failure to promptly and adequately address this matter may result in legal action without further notice including, without limitation, seizure and injunction. Unresolved deviations may also prevent other Federal agencies from awarding contracts.

We may re-inspect to verify that you have completed corrective actions to address any deviations.

This letter notifies you of our findings and provides you an opportunity to address the above deficiencies. After you receive this letter, respond to this office in writing within 15 working days. Specify what you have done to address any deviations and to prevent their recurrence. In response to this letter, you may provide additional information for our consideration as we continue to assess your activities and practices. If you cannot complete corrective actions within 15 working days, state your reasons for delay and your schedule for completion.

Please send your electronic reply to Compliance Officer Yvette Johnson at Yvette.Johnson@fda.hhs.gov, ORAPHARM1_RESPONSES@fda.hhs.gov and CDER-OC-OMQ-Communications@fda.hhs.gov. Identify your response with FEI 3013947845.

Sincerely,
/S/

Craig Swanson for Nerizza Guerin
Acting Program Division Director/ District Director
U.S. Food and Drug Administration
OPQO Division I / New Jersey District

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