January 12, 2022

Stephanie Durso, Director, Compliance Branch
Office of Pharmaceutical Quality Operations, Division I
10 Waterview Boulevard, Suite 300
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ORAPharm1_Responses@fda.hhs.gov

Subject: Response to FDA 483 Observations Issued to Dupont Nutrition USA, Inc. on December 15, 2021

Dear Ms. Durso,

On December 15, 2021, U.S. Food and Drug Administration (FDA) Investigators Craig Zagata and Kristina Conroy concluded an inspection of Dupont Nutrition USA, Inc. (FEI -3013947845) located in Newark, Delaware, USA and issued (8) Inspectional Observations on the form FDA-483. Attached are the observations and the corresponding responses.

Dupont Nutritional USA, Inc. acknowledges the concerns raised by the FDA in the Form 483 and takes seriously the significance of the observations. We are committed to taking all actions necessary to ensure our systems and documentation are compliant with requirements.

As is described in our attached detailed response, we have taken and are continuing to take actions to address each item. IFF has hired an external consultant to support our Corporate Quality Management and provide guidance during the review of our Quality Management System. In addition, IFF's Management team is committed to resourcing the sites to sustain the improvements. Our Corporate and Site Quality Leadership team is coordinating all corrective actions and necessary training within the Dupont Nutrition USA site. These corrective actions and training shall be completed by the deadlines indicated in the attached responses. In some cases, our ability to complete implementation is contingent on our ability to identify and hire qualified individuals considering COVID-related hiring challenges. IFF will proactively provide to FDA every (b)(4)) status reports starting March 2022 and as appropriate we will adjust our frequency of communication.

We trust that the actions described in this response convey our commitment to address the inspection observations in a comprehensive manner.

We would like to thank Investigator Zagata and Investigator Conroy for their professionalism during the inspection.
Should you have any other questions, please contact me at (610)844-6985.

Sincerely,

Matthew J. Davidson
Plant Manager, Pharma Solutions
Dupont Nutritional USA, Inc.
Newark, Delaware

C.C. Fred Flores, IFF VP Global Quality; Brian Albright, IFF VP of Operations; Craig Zagata, FDA Investigator

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Observation #1

Changes to established procedures were not reviewed to evaluate impact on product quality. Specifically, your firm discontinued review of data from inline conductivity meters without evaluating the impact on the quality of Avicel to be used as a drug component. These meters were used in Avicel microcrystalline cellulose (MCC) process validation studies to control conductivity of (b)(4) .

Commitment: Update MOC policy by 01/31/22.

Update: "Management of Change", EtQ document number 9134, was updated to Revision 3 per the description in our response letter and includes the addition of trigger criteria that more clearly define when an MOC is required. Please note, due to an administrative error, this document was not approved in our Document Control System (EtQ) until 02/09/22. See Exhibit 1. A supplemental "Quality Design Review Checklist" (EtQ document number 9231) was also created to be used during the Quality portion of MOC evaluation with an effective date of 02/04/22. See Exhibit 2. Training for the updated MOC procedure is ongoing and was committed for completion by 02/28/22.

Observation #2

Complaints are not adequately handled to determine the root cause to assure it does not recur and to detect product quality events that may warrant a recall.

Specifically, your firm did not perform meaningful data analysis of similar occurrences to detect potential trends and expand the scope of complaint investigations when warranted. For example, between April 2020 and May 2020 four customer complaints were received for out-of-specification (OOS) conductivity of Microcrystalline Cellulose (MCC), whereas for approximately a year prior there had been no customer complaints for OOS conductivity. Five more customer complaints occurred from that point until approximately November 2020 for OOS conductivity of MCC before the scope of the investigation was broadened.

Commitment: Conduct Management Review for Complaints by 03/31/22.

Update: Management Review for Complaints is scheduled for 02/24/22.

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Observation #3

Review of out-of-specification (OOS) results is not thorough enough to identify equipment or analyst errors.

Specifically, OOS investigations related to Avicel Microcrystalline Cellulose (MCC) are performed by the original analyst consisting of a review of tests performed. These reviews do not fully evaluate potential for human or equipment error.

Commitment: Update OOS Procedure and Checklists by 02/15/22.

Update: Out-of-Specification Laboratory Results Investigation procedure (EtQ document number 8961) was revised to Revision 2, OOS OOT Chemistry Investigation checklist was made a standalone document and titled "Chemistry Laboratory Investigative Report of an OOS_OOT Result" (EtQ document number 9236), and OOS OOT Microbiology Investigation checklist was made a standalone document and titled "Microbiology Laboratory Investigative Report of an OOS_OOT Result" (EtQ document number 9235). All three documents were updated with an effective date of 02/04/22 per the description in our response letter. These updates included separating the review into two parts. The initial review will be performed by the analyst and documented on the checklist. A secondary review/investigation will be performed by the lab supervisor and include verification of data and decision on the need for additional testing. The completed OOS investigation will be reviewed and signed by both the Lab Supervisor and a Reviewer from Quality Assurance. See Exhibits 3 (Sections 4.1.1.3, 4.1.2.1, and 4.1.2.1.1-4.1.2.2.6), 4 (page 2), and 5 (page 2) respectively. Training on the updated documents was completed on 02/14/22.

Observation #5

There was a failure to expand investigations into discrepancies to associated batches of drug products.

Specifically, your investigation into inaccurate readings of your conductivity meter/probe ((b)(4)), used for Avicel microcrystalline cellulose (MCC) conductivity testing, was not expanded to include all lots of drug product that were tested by the meter/probe and subsequently released. The meter/probe was used to conduct release testing on lots 2173811666 and 2173802516 immediately prior to the discovery of the discrepancy. No additional testing was performed on these lots as part of the investigation into the inaccurate readings.

Commitment: Update Lab Investigation Procedure by 02/15/22.

Update: Laboratory Minor Incident procedure (EtQ document number 8956) was updated to Revision 2 with an effective date of 02/15/22. Additionally, Laboratory Incident Report form was made a standalone document and titled "Laboratory Minor Incident Form" (EtQ document number 9241) with an effective date of 02/04/22. Both documents were updated to require a documented assessment of impact on additional lots (if any). See Exhibits 6 (Section 4.2) and 7 (page 2) respectively. Training on these documents was completed on 02/14/22.

Observation #6

Batch records do not include complete information relating to the production and control of each batch.
Specifically, batch release by the Quality Unit does not include the review of all relevant production records, including critical in-process parameters, to confirm that the process remained in a state of control, and to identify discrepancies, including process disrupts, during operations that may require further evaluation to assess the adequacy of the finished product being released.

Commitment: Implement a form for reporting process deviations/upsets to the Quality Unit by 01/31/2022.

Update: To quickly address this observation, a "Process Upset Form" was created to document process deviations/upsets that occur during manufacturing and includes a section for the Quality Unit to document impact on product quality. Since a procedure for use of this form is not yet in place, this form was implemented through the MOC process (MOC 11500, approved 01/28/22). Use of the form will be proceduralized by 03/31/22 as previously committed. See Exhibit 8 for MOC 11500 and Exhibit 9 for the "Process Upset Form".

Observation #7B

Laboratory controls were not followed and documented at the time of performance. The quality checks were not completed prior to use for microbiological media used in finished product testing. Departures from the procedure were not documented and explained. Your Microbiology Technician retrospectively back dated the completion of the quality checks for the media during the inspection.

Commitment: Update Completion of Handwritten Documents Procedure by 02/15/2022.

Update: Completion of Handwritten Documents Procedure (EtQ document number 4710) was updated, inclusive of a documented title change, to Revision 12, "Good Documentation Requirements for GMP Records," with an effective date of 02/04/22. The update includes the principles of ALCOA as well as instructions on how to address records that were not properly completed at the time of the activity. Please refer to Section 4.0 ALCOA Principles and Section 7.0 Correcting Errors in Records in Exhibit 10. Training on the updated document was completed by 02/14/22.

Commitment: Define frequency for monitoring errors in GMP records by 02/15/2022.

Update: Dupont Nutrition USA, Inc will monitor errors in GMP records by using Quality personnel from our Continuous Improvement teams to perform verification audits on both in-process and completed GMP documentation through the end of 2022. A sampling of GMP documentation from each area (Operations, Maintenance, and Quality) will be audited for compliance to our updated procedure. At least 100 documents will be audited per (b)(4) Auditing is scheduled to begin the week of 02/21/22. To ensure training was effective, auditing will initially occur (b)(4)

As improvement is observed, the frequency of these effectiveness check audits and quantity of documents audited will be decreased. Reference Exhibit 11 for the GMP Documentation Audit Schedule through March 2022.

Commitment (as expressed in original 483 Response)**:** "We will review lab investigations involving failed quality checks on microbiological media for the past 4 years to evaluate whether the media were used for any lot testing. If failing media was used, we will ensure appropriate consideration was given to impact on lots tested since the last successful calibration, and address issues that may be identified based on the risk to patient safety. This review will be completed by 03/31/2022."

Update: Dupont Nutrition USA is currently working towards completion of this action. However, we wanted to note that there was an error in the commitment as presented in the original 483 response. The updated commitment is below with the correction **bolded and underlined** for clarity.

"We will review lab investigations involving failed quality checks on microbiological media for the past 4 years to evaluate whether the media were used for any lot testing. If failing media was used, we will ensure appropriate consideration was given to impact on lots tested **using the failed media**, and address issues that may be identified based on the risk to patient safety. This review will be completed by 03/31/2022."

Observation #7C

Laboratory records containing analytical and microbiological testing for product release determinations do not include documentation showing that the sample preparation is in conformance with test requirements for all tests performed on each lot. For example, sample preparation weights and equipment used are not documented for microbiological testing.

Commitment: Define and start Implementation of interim measures for recording sample weight & equipment/instrument IDs

Update: A template for Laboratory equipment logbooks was created to capture Equipment ID, Sample ID, Product Name, Test, Sample weight, Date, and Analyst Initials. Since a procedure for use of this logbook template is not yet in place, this logbook template was implemented through the MOC process (MOC 11500, approved 01/28/22, Exhibit 8) to be used at balances in the main chemistry lab for finished product testing and is attached as Exhibit 12. Formalized worksheets and/or logbooks for recording of sample preparation details are being developed and will be implemented once finalized.

February 15, 2022

Stephanie Durso, Director, Compliance Branch
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Subject: Update to Response to FDA 483 Observations Issued to Dupont Nutrition USA, Inc. on December 15, 2021 (FEI 3013947845)

Dear Ms. Durso,

On December 15, 2021, U.S. Food and Drug Administration (FDA) Investigators Craig Zagata and Kristina Conroy concluded an inspection of Dupont Nutrition USA, Inc. (FEI 3013947845) located in Newark, Delaware, USA and issued (8) Inspectional Observations on the form FDA-483. On January 21, 2022, we submitted our response to those observations and committed to providing the FDA with regular updates.

Attached is the first update to our committed actions resulting from the FDA-483. Only responses with one or more actions completed since the original response to the 483 are included in this update. We are also attaching a table, "FDA 483 Response Commitment Table," showing the status of all corrective actions.

Updated documents are included as Exhibits. Relevant changes made to existing documents have been highlighted in yellow and cross-referenced in the "Attachment for 483 Response - Feb 2022 Update" document.

This update is provided to show ongoing progress towards the actions we have committed to complete. The first committed (b)(4) update will be provided by 03/31/22.

Should you have any other questions, please contact me at (610)844-6985.

Sincerely,

Matthew J. Davidson
Plant Manager, Pharma Solutions
Dupont Nutritional USA, Inc.
Newark, Delaware

C.C. Fred Flores, IFF VP Global Quality; Brian A bright, IFF VP of Operations; Craig Zagata, FDA Investigator

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Observation #1

Changes to established procedures were not reviewed to evaluate impact on product quality. Specifically, your firm discontinued review of data from inline conductivity meters without evaluating the impact on the quality of Avicel to be used as a drug component. These meters were used in Avicel microcrystalline cellulose (MCC) process validation studies to control conductivity of (b)(4)

Commitment: Once the new policy is finalized and entered into our document management system, we will train all relevant site personnel on the revised policy by 02/28/2022.

Update: The "Management of Change" procedure was updated and approved as indicated in our Response update provided on 02/15/22. Training on this procedure was executed over eight (8) sessions and given to personnel in Quality, Plant Management, Operations, Engineering, and EHS. The final training session was completed on 02/28/22.

Commitment: To mitigate the potential that other changes have already been made to the process of manufacturing MCC, without adequate review, we will evaluate the other quality critical parameters listed in our most current validation. We will verify that we continue to operate under those parameters, or, where we have made a change, that it was properly implemented using our MOC process with an evaluation for impact on product quality. Where we cannot locate adequate documented justification for a lack of impact on product quality, we will retrospectively evaluate based on our product shelf life and document the impact. Based on the results of this activity, we will evaluate and document impact on pharma grade Avicel® microcrystalline cellulose (MCC) lots manufactured under conditions where quality critical parameters as defined in the current process validation were not met. We have started these evaluations and will communicate our completion date for this activity in our first (b)(4) update to FDA.

Update: We have identified the differences between current operations and the most recent process validation. We are currently in the process of reviewing the historic MOC documentation to determine if quality impact was considered during the changes that were implemented. The MOC review and subsequent retrospective evaluations (if needed) will be completed by 06/30/22.

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Commitment: Complete planning phase for revalidation of MCC and communicate the planned completion date for the revalidation in our first (b)(4) update.

Update: The planning phase for the revalidation of MCC was completed by 03/22/22. The MCC process consists of several unit operations, which will be revalidated separately. The revalidation of all MCC unit operations will be completed by December 2022.

Observation #2

Complaints are not adequately handled to determine the root cause to assure it does not recur and to detect product quality events that may warrant a recall.

Specifically, your firm did not perform meaningful data analysis of similar occurrences to detect potential trends and expand the scope of complaint investigations when warranted. For example, between April 2020 and May 2020 four customer complaints were received for out-of-specification (OOS) conductivity of Microcrystalline Cellulose (MCC), whereas for approximately a year prior there had been no customer complaints for OOS conductivity. Five more customer complaints occurred from that point until approximately November 2020 for OOS conductivity of MCC before the scope of the investigation was broadened.

Commitment: The [Customer Complaint] procedure will be revised to include additional instructions on how to determine if a complaint is related to a current or previous investigation and when subsequent actions are required. The updated procedure will also clarify that customer complaint trending will be executed per the requirements of the updated management review procedure, described below.

> **Update:** "Customer Complaint Handling Procedure", EtQ document number 9103, was updated to Revision 3 per the description in our response letter and includes instruction for consideration of the following: other customer complaints against the complaint lot, and other complaints that are similar/related in nature (Section 6.3: Complaint Investigation). The *Customer Complaint Handling Procedure* was also updated to state that customer complaints are reviewed according to the Management Review requirements in Section 7.2. See Exhibit 1. After utilizing the updated "Customer Complaint Handling Procedure," additional opportunities for clarifying the complaint leveling were apparent. The procedure was therefore updated to Revision 4. Reference Exhibit 2. A standalone job aid, "Job Aide for Customer Complaint Trending", EtQ document number 9314, was created to provide a detailed explanation as to how customer complaints should be trended to identify potentially recurring complaints. See Exhibit 3. Training was provided to relevant personnel for each document update.

Commitment: Update Complaint Checklist to increase thoroughness of the investigation and level of detail that is documented.

> **Update:** The "Complaint Checklist" was updated per the description in our response letter to increase thoroughness of the investigation and the level of detail that is documented. The checklist was made a standalone document and titled "Complaint Investigation Form" (EtQ document 9277). See Exhibit 4. Based on the clarifications made to the "Customer Complaint Handling Procedure," aligning clarifications were made to the "Complaint Investigation Form" (removal of the choice for Level 1 and Level 2 in the "Complaint Classification" section) and the document was updated to Revision 2. See Exhibit 5. Training was provided to relevant personnel for each document update.

Commitment: The site's Management Review procedure will be updated to require at least (b)(4) trending of complaints. It will also include more detailed explanation of the required elements for trending so that recurring nonconformances are identified and addressed.

Update: "Management Review" procedure, EtQ document number 8962, was updated to Revision 2 per the description in our response letter and includes at least (b)(4) trending of Customer Feedback (i.e. customer complaints). See section 3.2 of Exhibit 6. A standalone job aid, "Job Aide for Customer Complaint Trending", EtQ document number 9314, was created to provide a detailed explanation as to how customer complaints should be trended. See Exhibit 3.

Commitment: Further evaluate product quality customer complaint data for the past 24 months to determine the thoroughness of the investigations and effectiveness of the corrective actions.

Update: Customer complaint data for 2020-2021 was reviewed to determine effectiveness and perform trend analysis. There were no quality critical trends identified and the analysis of the data was discussed during the Management Review Meeting referenced in the next commitment.

Commitment: Conduct Management Review for Complaints by 03/31/22.

Update: Management Review for Complaints was held on 03/09/22. Participants in the meeting included representatives from: Quality, Plant Management, Operations, Engineering, and EHS. A summary of both the agenda and meeting minutes is provided below.

Agenda	• High-level discussion of FDA-483 observation regarding customer complaints • Customer Complaint data review for 2020 and 2021 • Trend Discussion • Determine Action Plan

Meeting Summary:

Data that was reviewed for 2020-2021 highlighted that complaints related off-color particles (OCPs) continue to occur, as seen in previous years. The majority of OCPs were classified as technically unavoidable particles (TUPs). Most TUPs in products manufactured at Newark are traced back to variations in our wood pulp raw material and pose no risk to human health.

The results of the complaint review did not identify any critical concerns for product quality. However, continuous improvement discussions have identified areas for improvement relating to the review of leading indicators. To ensure continuous review of customer complaint data, an action was created to establish the schedule and format for periodic customer complaint data review that is shared with the site.

Observation #4

Your recall procedure does not clearly define the conditions that necessitate a recall so that it may be executed in a consistent and effective manner.

Specifically, your procedure has recall requirements if there are potential health hazards or if violations of law exist but does not adequately define what constitutes these circumstances. Your procedure does not clearly define recalling distributed products later found to be out-of-specification.

Commitment: We will update the procedure to provide clearer roles and responsibilities as well as examples incorporating IFF product types and situations that would lead to stock recovery, market withdrawal or recall. Our updated procedure will explain different factors and circumstances that need to be considered when making a recall decision.

Update: "Product Recall and Mock Recall Procedure", EtQ document number 8881, was updated to Revision 2 per the description in our response letter. The updates include clearer roles and responsibilities (Section 4 and Appendix A), IFF specific examples for product recall types (Sections 3.2, 3.3, and 3.4), and an explanation of the different factors and circumstances that need to be considered when making a recall decision (Appendix A). See Exhibit 7. Additional clarification needs specifying the considerations for notifying regulatory authorities were identified after the "Product Recall and Mock Recall Procedure" procedure was approved as Revision 2. Therefore, the document was updated to Revision 3 to include this specificity (Section 1 and Appendix A, ID 3). See Exhibit 8.

Commitment: A checklist of required actions will be created to ensure activities associated with a recall are consistently and effectively executed.

Update: A new recall checklist document was created to ensure activities associated with a recall are consistent and effective. The document is titled "Product Recall Checklist" and its EtQ document number is 9284. See Exhibit 9.

Observation #6

Batch records do not include complete information relating to the production and control of each batch.
Specifically, batch release by the Quality Unit does not include the review of all relevant production records, including critical in-process parameters, to confirm that the process remained in a state of control, and to identify discrepancies, including process disrupts, during operations that may require further evaluation to assess the adequacy of the finished product being released.

Commitment: We are performing a new risk assessment of the MCC production process in order to ensure that quality-critical parameters and their ranges, where applicable, are properly identified. We will complete this risk assessment by 02/28/2022.

Update: A process FMEA was conducted on the Avicel® MCC product lines: PH-101, PH-102, and PH-200. The risk assessment was completed by 02/28/22 and included participants from Operations, Engineering, R&D, and Quality. The findings from the risk assessment will be incorporated into the revalidation activity related to Observation 1.

March 25, 2022

Stephanie Durso, Director, Compliance Branch
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Subject: Update to Response to FDA 483 Observations Issued to Dupont Nutrition USA, Inc. on December 15, 2021 (FEI 3013947845)

Dear Ms. Durso,

On December 15, 2021, U.S. Food and Drug Administration (FDA) Investigators Craig Zagata and Kristina Conroy concluded an inspection of Dupont Nutrition USA, Inc. (FEI 3013947845) located in Newark, Delaware, USA and issued (8) Inspectional Observations on the form FDA-483. On January 12, 2022, we submitted our response to those observations and committed to providing the FDA with regular updates.

Attached is the first (b)(4) update to our committed actions resulting from the FDA-483. Only responses with one or more actions completed since the last response to the 483 (dated 02/15/22) are included in this update. We are also attaching a table showing the status of all corrective actions.

Updated documents are included as Exhibits. Relevant changes made to existing documents have been highlighted in yellow and cross-referenced in the “Attachment for 483 Response - Mar 2022” document.

This update is provided as part of our committed actions and to show ongoing progress towards completed actions.

Additionally, I would like to inform you that I have accepted a new position within the organization and moving forward, the new Plant Manager, Greg Sherman, will be providing regular updates.

Should you have any other questions, please contact Greg at (616)502-0598 or (b) (6).

Sincerely,

Matthew J. Davidson
Plant Manager, Pharma Solutions
Dupont Nutritional USA, Inc.
Newark, Delaware

C.C. Fred Flores, IFF VP Global Quality; Brian A bright, IFF VP of Operations; Craig Zagata, FDA Investigator

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