SUMMARY

This inspection of a drug component manufacturer was conducted in response to eNspect OPID 205195 and For Cause Inspection Request from CDER (see Assignment Memo dated 09/07/2021 as Attachment 3). This inspection was performed in accordance with Compliance Program 7356.002, Drug Manufacturing Inspections. Coverage was afforded to the Quality, Production and Laboratory systems specific to inspecational memo information requests.

The previous FDA inspection dated 06/10/2010 was classified NAI and did not result in the issuance of a Form FDA-483, additionally no discussion items were presented.

The current inspection revealed that the firm continues to function as a manufacturer of excipient for use in human drug products. The inspection concluded on 12/15/2021 and resulted in the issuance of an 8 item Form FDA-483, Inspectational Observations for:

1. Failure to evaluate impact of change on validated process.
2. Failure to adequately investigate complaints.
4. Recall procedure does not adequately define conditions necessitating a recall.
5. Failure to expand investigations of discrepancies to include associated batches.
6. Batch records review does not include review of critical in-process parameters.
7. Failure to include all laboratory data in laboratory control records.
8. Failure to verify analytical methods were suitable for actual use conditions.
A discussion item was presented for:

- Vague procedures that do not clearly indicate personnel responsible for performing task or the criteria that determine which tasks need to be performed.

No samples were collected, and no refusals encountered. Management indicated that intended to respond to observations on the Form FDA-483. They further indicated they would contact the agency to request an extension due to the upcoming holiday.

**ADMINISTRATIVE DATA**

<table>
<thead>
<tr>
<th>Administrative Data</th>
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<tr>
<td><strong>Firm</strong></td>
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<td><strong>Physical Address</strong></td>
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<td>Address Line 1</td>
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<td>City / State / ZIP</td>
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<td><strong>Phone</strong></td>
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<td><strong>Fax</strong></td>
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<td><strong>Email Address</strong></td>
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<tr>
<td><strong>Inspection Date(s)</strong></td>
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<td><strong>Days at the Facility</strong></td>
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**FDA Inspection Participants**

<table>
<thead>
<tr>
<th>Participant Name and Title</th>
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<tbody>
<tr>
<td>Craig D. Zagata, Investigator</td>
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<tr>
<td>Kristina L. Conroy, Investigator</td>
</tr>
<tr>
<td>LCDR Sayyem Akbar, Investigator</td>
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**Issued 482 Forms**

On the date(s) below, credentials were presented and a "Form FDA 482, Notice of Inspection" (attached) was issued to the person listed.

<table>
<thead>
<tr>
<th>Date Issued</th>
<th>Issued To</th>
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</thead>
<tbody>
<tr>
<td>11/17/2021</td>
<td>Matthew J. Davidson, Plant Manager</td>
</tr>
</tbody>
</table>

On 11/17/2021 Investigator Sayyem Akbar, Investigator Kristina L. Conroy and I (Investigator Craig D. Zagata) presented our credentials and issued a Form FDA-482, Notice of Inspection (Attachment 1) to Matthew J. Davidson who identified himself as the most responsible individual at the firm.
Establishment Inspection Report

FEI: 3013947845
Dürron Nutrition USA, Inc.
Newark DE, 19711

EI Start: 11/17/2021
EI End: 12/15/2021

Investigators were on site as follows:

<table>
<thead>
<tr>
<th>Investigator</th>
<th>Dates on site</th>
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</thead>
<tbody>
<tr>
<td>Craig D. Zagata</td>
<td>11/17-11/19/21, 11/22-11/24/21, 11/30-12/01/21, 12/13/21, 12/15/21</td>
</tr>
</tbody>
</table>

On 12/15/2021 a closeout meeting was held with firm personnel; a Form FDA-483, Inspectional Observations (Attachment 2) was issued to Matthew J. Davidson. Mr. Davidson indicated the firm intended to respond to the FDA-483.

HISTORY

(SA)

According to Mr. Moore, in 1962 the Newark plant-initiated startup operations. In 1963 FMC purchased American Viscose and Avicel® MCC was commercialized for pharmaceutical use. In 1968 the plant expanded to produce colloidal Avicel®. In 1986 the firm started up coatings and by 1992 the plant was ISO certified. By 1993 the firm was producing specialty grades of Avicel®. In 1999 FMC Biopolymer Division was formed by Pharmaceutical & Food Ingredients Divisions and the purchase of ProNova from Norsk Hydro. In 2003 the firm completed ISO 9001:2000 certification and C-TPAT certification, by 2005 the firm was Responsible Care certified. The firm’s most recent certifications are GMA Safe; and ISO 9001:2015.

The firm is not registered with the FDA as a drug firm.

The firm was incorporated in the state of Delaware in 1928.

The firm’s corporate headquarters is located at 521 West 57th Street, New York, NY 10019.

The firm has approximately 2044 employees and production operates (b)(4). Office business hours are 8:00 AM to 4:30 PM.

On November 1, 2017, the division was sold from FMC to DuPont. It merged into the health nutrition department of DuPont. The firm existed that way for three-and-half years.

On February 1, 2021, the nutrition of biosciences division left DuPont and merged into International Flavors & Fragrances Inc. (IFF), a USA based company.
In 2020, the firm sold (b)(4) worth of pharmaceutical products and (b)(4) worth of food products.

All FDA correspondence should be addressed as follows:

Matthew Davidson, Plant Manager  
1301 Ogletown Road  
Newark, DE 19711

**JURISDICTION / INTERSTATE COMMERCE**

(SA)  
According to Mr. Davidson, the firm produces the following drug components:

- Avicel® PH/PC Microcrystalline Cellulose
- Avicel® RC/CL/PC Microcrystalline Cellulose and Carboxymethylcellulose Sodium
- Avicel® CE Microcrystalline Cellulose and Guar Gum
- Avicel® HFE Microcrystalline Cellulose and Mannitol
- Endurance® VE Microcrystalline Cellulose
- Vitacel® VE Microcrystalline Cellulose and Calcium Carbonate
- Aquacoat® ECD-30 Ethylcellulose Aqueous Dispersion
- Aquacoat® ARC Alcohol Resistant Coating
- Aquacoat® CPD-30 Cellulose Acetate Phthalate Aqueous Dispersion
- Ac-Di-Sol® Croscarmellose Sodium
- Accelerate® Modified Cellulose Gum

The firm’s products are listed and detailed on Excipient Information pack – Product Regulatory Data Sheet (Exhibit 40).

According to Mr. Davidson, the firm receives wood pulp, it’s main raw material from (b)(4) |

**INDIVIDUAL RESPONSIBILITY AND PERSONS INTERVIEWED**

(SA)  
The firm’s organizational chart is included as Exhibit 41.

Matthew James Davidson - Plant Manager - According Mr. Davidson, he has been with DuPont for approximately 7 years and in his current role for 4 years. Responsibilities include EHS, production, quality improvement and related activities. He reports to Brian Albright, Vice President of Pharma
Operations and Supply Chain. He has 6 direct reports and was present at the opening and closeout meetings. He provided information and was the most responsible person for the site.

**Patricia McDermitt - Quality Manager** - According to Ms. McDermitt, she has been with DuPont for 36 years and in her current role for 4 years. Responsibilities include oversight of site QA, complaints, releases, third party certifications and QC laboratories. She reports to Matt Davidson with a dotted line to Kieran O'Dwyer, Quality Leader for Pharma Solutions (Maine). She has 4 direct reports and was present at the opening and closeout meetings. She provided information and documentation during the inspection.

**Joshua Stevens - Associate Quality Manager** - According to Mr. Stevens, he has been with DuPont for 28 years and in his current role for 4 years. Responsibilities include supplier quality and supporting quality at pharma solution plants. He reports to Kieran O'Dwyer, Quality Leader for Pharma Solutions (Maine). He does not have any direct reports. He acted as a scribe during the inspection.

**Ann Gulau - Quality Manager** - According to Ms. Gulau, she has been with DuPont for approximately 34 years and in her current role for 5 years. Responsibilities include oversight of quality at the business/pharma solutions level, customer quality agreements, assisting with issues and audits at the site, and IPEC representative. She reports to Kieran O'Dwyer, Quality Leader for Pharma Solutions (Maine). She does not have any direct reports. She participated in the teleconference on DuPont’s recall (No. 88617) on Friday (11/19/21) and was present during the inspection on 11/22/21, 11/23/21, 11/30/21, and 12/01/21.

During the inspection, the open position of the Quality Improvement Engineer was filled by Jocelyn Victor. Ms. Victor's starting date was 11/29/21. She was present at the meetings from 11/30/21 onward.

During the inspection, the following firm personnel provided information and documentation:

- Brian Albright – VP Operations – Manufacturing
- (b) (6) – Process Development Engineer
- Jennifer Laracy – Global Director QMS and CI
- Kieran O’Dwyer – Quality Leader Pharma Solutions Business
- (b) (6) – Americas Logistics Leader
- Priscilla Sager Zawislak – Associate EH&S Regulatory Manager
- William Burgoon – Distribution Manager
- Ian Ertle – Coatings and Logistics Area Manager
- (b) (6) – Release Coordinator
- (b) (6) – Chemical Technician
- (b) (6) – Microbiology Technician
- (b) (6) – Quality Improvement Leader
FIRM’S TRAINING PROGRAM

I reviewed the procedure PR-NWK-0005 entitled, “Training & Development”, Revision 16, effective date 08APR2019, without comment. The procedure provides guidelines for the training of all employees onsite at the firm. Training is documented utilizing an electronic Sharepoint Database and consists of position specific training matrixes. The firm has three levels of training which include: (1) Read and understand, (2) On the Job Training, and (3) Classroom training. According to procedures PR-NWK-0000-18 entitled, “GMP Training”, Revision 2, effective date 07SEP2021 and PR-NWK-0000-19 entitled, “cGMP Training Guideline, New Employee”, Revision 1, effective date 07SEP2021, cGMP training is performed during new employee orientation and at a minimum once per year. I reviewed cGMP training records for [redacted] without comment.

MANUFACTURING/DESIGN OPERATIONS

Quality System

Finished Product Release-Microcrystalline Cellulose (MCC)

The firm’s procedure PR-NWK-0000-016 (8969) “Finished Product Release”, Revision 1, effective date 24AUG2021 (Exhibit 1 pages 1-5) describes the process of releasing finished product for distribution to customers. Quality Assurance personnel are required to review paper and electronic records and document the review on the “Batch Record Review Checklist”. According to PR-NWK-0000-016, Quality Assurance personnel release the product in LIMS and [redacted] after completing the Batch Record Review Checklist (See Objectionable Conditions Item 6).

Out-of-Specification Microbial Investigations

I reviewed the microbiological investigation summary (Exhibit 33 pages 17-31), OOS Microbiology Laboratory Investigation Report (Exhibit 32 pages 5-6), DEV-03521 and CAPA-00412 for RC591 (Exhibit 38) NF Lot 217376940 drum #151 failure of internal specification of [redacted] for Total Aerobic Microbial Count (TAMC). The organism recovered was Micrococcus luteus. The Microbiology Laboratory Investigative Report for the OOS concluded no assignable cause for the OOS related to the microbiology laboratory and personnel. A product [redacted] sampling was performed on drum [redacted] through [redacted] and [redacted] through [redacted]. The drums were tested for the TAMC microbiological parameter only and recovered less than or equal [redacted]. The investigation concluded a probable cause of human contamination of the sample itself and corrective action was to retrain operators on proper technique when obtaining microbiological samples.
I reviewed the microbiological investigation summary (Exhibit 31 pages 15-21), OOS Microbiology Laboratory Investigation Report (Exhibit 3 pages 83-84), QIR 07092020 and CAPA-00376 (Exhibit 31 pages 23-39) for MCC PH 200 NF Lot 2173728724 drum 1001 failure of internal specification of absence of coliforms. The organism recovered was *Pantoea* species. The Microbiology Laboratory Investigative Report for the OOS concluded no assignable cause for the OOS related to the microbiology laboratory and personnel. A product sampling was performed on drum through and through The drums were tested for the coliform microbiological parameter only and did not recover *Pantoea* species. The investigation concluded a probable cause of human contamination of the sample itself and corrective actions included to retrain operators on cleaning and sanitization with focus on high contact points.

I reviewed the following investigation procedures:


I observed that the firm’s investigation procedures, PR-NWK-0000-033, PR-NWK-0000-026 and PR-NWK-0000-034, lacked clearly defined actions to ensure the consistent performance of a well-documented comprehensive analysis. I commented that when assessing the impact and potential root cause of microbial contamination that it may be warranted to expand the assessment beyond containers directly before and after the failed containers, and to evaluate microbiological parameters that passed specification, but may still have had growth present. Ms. Patricia McDermitt, Quality Manager acknowledged my comments.

**Production System**

*(KLC)*

*Control of Microcrystalline Cellulose (MCC)*

The firm manufactures Microcrystalline Cellulose (MCC) using a process with dedicated equipment. Production is run in and within several lots are produced. A lot varies depending on package type and the stock keeping unit (SKU) in Procedure PR-NWK-0305-007 (8693) “Controlling the MCC Process for NF Material”, Revision 1, effective date 09APR2021 (Exhibit 2 pages 1-12) provides guidelines for controlling the MCC for compendial (NF) material and making process adjustments. PR-NWK-0305-007 includes several different process adjustments based on actions limits and control limits of critical and non-critical parameters. The Senior Manufacturing Operator (SMOII) makes system adjustments to keep the product within limits. PR-NWK-0305-007 identifies conductivity as a critical parameter and action is be taken if control
limits are exceeded or values are off target. Mr. Matthew Davidson, Plant Manager stated that conductivity of MCC is controlled through \( \text{(b)(4)} \) and \( \text{(b)(4)} \) operations. Procedure PR-NWK-0301-008 (8708) entitled, \( \text{(b)(4)} \), Revision 2, effective date 23JUL2021 describes the operation of the \( \text{(b)(4)} \) system (Exhibit 2 pages 13-37). Per PR-NWK-0301-008 the Shift Supervisor is responsible for maintaining records of the \( \text{(b)(4)} \) operations. The SMOII operates the \( \text{(b)(4)} \), completes \( \text{(b)(4)} \) records, reviews Product Manufacturing Conditions Specifications at the start of shift to check for changes that may have been made to the original operating conditions to obtain optimum operation.

**Reprocessing- Microcrystalline Cellulose (MCC)**

Procedure PR-NWK-0201-009 entitled, “Reprocess Guideline for Newark Finished Products”, Revision 17, dated 29JAN2018 (Exhibit 30 pages 9-11) provides guidelines for reprocessing Microcrystalline Cellulose (MCC). MCC can either be \( \text{(b)(4)} \). According to PR-NWK-0201-009, MCC \( \text{(b)(4)} \).

Per PR-NWK-0201-009 product can be \( \text{(b)(4)} \) when the steps taken will correct the failure, and includes material that is downgraded for pH, conductivity, water solubles, loss on drying (LOD), particle size distribution (PSD), sieve, and loose bulk density (LBD). \( \text{(b)(4)} \). Procedure PR-NWK-0202-009 entitled “750 Reprocessing System Operation”, Revision 12, dated 07AUG2019 (Exhibit 30 pages 1-3) outlines the steps to operate the reprocessing system to recover MCC.

**Laboratory System**

(KLC)

**Analytical Equipment**

I reviewed the following analytical equipment qualification reports:

- TM18004N entitled, “\( \text{(b)(4)} \) Particle Size Distribution Analyzer Validation”, Dated 20DEC2018.

No significant concerns were noted.

**Calibration-Conductivity Meters**

I evaluated the firm’s conductivity meter calibration procedures and practices. According to the method in use in 2020, \( \text{(b)(4)} \) entitled, “Conductivity Meter Operation and Calibration”,
Revision 1 (Exhibit 29 pages 9-12), the quality control laboratory conductivity meters were required to be calibrated every (b)(4). I reviewed the firm’s 2020 Conductivity Meter Calibration Forms and noted no significant deficiencies. Quality Assurance personnel opened DEV-04008 and CAPA-00456 (Exhibit 26 pages 1-9) on 14DEC2020 because the (b)(4) Conductivity Meter, used for product testing of Microcrystalline Cellulose (MCC), showed poor response time when stabilizing. Action items included replacing the (b)(4) Conductivity Meter with (b)(4) and modifying method (Exhibit 26 pages 11-28).

I reviewed the method currently in use, (b)(4) entitled “Conductivity Meter Operation and Calibration”, Revision 4, effective date 31AUG2021 (Exhibit 29 pages 1-7), and the last 6 months of associated calibration records. I noted no significant deficiencies. Modifications to method (b)(4) included an increase in the frequency of calibration. According to method (b)(4) Revision 4, (b)(4) are required to be calibrated, while meters (b)(4) and (b)(4) are required to be calibrated (b)(4) with the (b)(4) standard. Additionally, method (b)(4) Revision 4 includes (b)(4) verification checks with a range of four standards from (b)(4) on all (b)(4) meters and on meter (b)(4) using an Avicel Reference Standard sample. Probes are replaced minimally every (b)(4). According to method (b)(4) Revision 4, the meters are dedicated for specific testing as follows: Meter (b)(4) for testing samples using the (b)(4) method, Meter (b)(4) for conductivity testing using the compendial method, Meter (b)(4) for process (b)(4) testing, and Meter (b)(4) for testing conductivity of colloidal materials.

Test Methods-Microcrystalline Cellulose (MCC)

I reviewed the firm’s Master Validation Plan No. MP98001N-01 entitled “Validation Master Plan for the FMC Biopolymer Newark Plant (FMCBN)”, dated 19APR2000, (Exhibit 18) and procedure PR-NWK-0012-002 entitled, “Test Method Validation”, Revision 6, effective date 31MAY2018 (Exhibit 19) without comment.

Microbiological Test Methods

I reviewed the following microbiological methods (Exhibit 9) used for testing Microcrystalline Cellulose (MCC):

- (b)(4) entitled, “Micro-Yeast and Mold Enumeration”, Revision 1, Effective Date 23APR2020.
- (b)(4) entitled, “Micro-Total Aerobic Microbial Count”, Revision 1, Effective Date 23APR2020.
- (b)(4) entitled, “Staphylococcus Aureus, Isolation and Identification”, Revision 1, Effective Date 24APR2020.
- (b)(4) entitled, “Micro-Test for Salmonella Species” Revision 1, Effective Date, 24APR2020.
- (b)(4) entitled “Micro-Escherichia Coli, Isolation and Identification”, Revision 1,
Establishment Inspection Report

Dupont Nutrition USA, Inc.
Newark DE, 19711

FEI: 3013947845
EI Start: 11/17/2021
EI End: 12/15/2021

Effective Date 24APR2020.

- [b](4) entitle, “Micro-Pseudomonas aeruginosa, Isolation and Identification” Revision 1 Effective Date 23APR2020.
- [b](4) entitle, “Micro-Coliform Enrichment”, Revision 1, Effective Date 27APR2020.

Additionally, I reviewed the validation report for microbial method suitability for MCC, TM13007N entitled, “Microbial Enumeration Tests and Test for Specified Organisms-MCC”, dated 2013. No significant deficiencies were noted.

Analytical Test Methods
I reviewed the following analytical methods (Exhibit 10) used for testing Microcrystalline Cellulose (MCC):

- [b](4) entitle, “Avicel MCC, pH and Conductance USP-NF and EP”, Revision 2, Effective Date 23MAR2021.
- [b](4) entitle, “Avicel MCC pH and Conductance 15%”, Revision 2, Effective Date 23MAR2021.
- [b](4) entitle, “Avicel MCC, Residue on Ignition, Ph.Eu.”, Revision 1, Effective Date 26MAR2020.
- [b](4) entitle, “Avicel MCC, Near IR”, Revision 1, Effective Date 27MAR2020.
- [b](4) entitle, “Avicel MCC Infrared Identification”, Revision 1, Effective Date 27MAR2020.
- [b](4) entitle, “Avicel MCC Water Solubles”, Revision 1, Effective Date 27MAR2020.
- [b](4) entitle, “Avicel MCC Heavy Metals, Ph.Eur.”, Revision 1, Effective Date 27MAR2020.
- [b](4) entitle, “Avicel MCC Ether Soluble Substances”, Revision 1, Effective Date 27MAR2020.
- [b](4) entitle, “Avicel MCC Assay”, Revision 1, Effective Date 26MAR2020.
- [b](4) entitle, “Avicel MCC, Fiber Content” Revision 1, Effective Date 27MAR2020.

Additionally, I reviewed the validation protocols and reports without comment:

Establishment Inspection Report

Dupont Nutrition USA, Inc.  
Newark DE, 19711

FEI: 3013947845  
EI Start: 11/17/2021  
EI End: 12/15/2021

- TM00037N entitled, “NF Identification Test”, Effective Date 06DEC2000.

Conductivity Test Method Validation

I reviewed Validation Report VR-2021-000005 entitled, “Conductivity of Microcrystalline Cellulose”, dated 14APR2021 (See Objectionable Conditions Item 8). Validation Report VR-2021-000005 is a compilation of the analysis of four studies, which included one instrument accuracy study, one correlation study, and two precision studies. Ms. McDermitt confirmed that there was not a test protocol associated with Validation Report VR-2021-000005. Two precision studies, with one lot of PH 101 MCC for each study, were performed using the compendial method. The quality control laboratory at Newark, Delaware USA performed a conductance measurement comparison study between the quality control laboratory at the Cork, Ireland facility. The report entitled, “Conductance Measurement Comparison: Comparison Between Cork & Newark”, dated 20JAN2021 (Exhibit 20) stated the purpose of the study was to evaluate the difference between the conductivity measurements between the two quality control laboratories. A single sample of PH101 MCC was divided between the Cork and Newark quality control labs with each lab performing tests using operators to run tests. The quality control laboratory in Cork used a model with probe and in Newark used the model with probe. The average conductivity measurement for the single lot of PH101 MCC that was tested was .

According to Validation Report VR-2021-000005, an additional sample, sample of PH101 MCC was analyzed at the firm’s quality control laboratory over a period using two analysts. The average conductivity measurement for the single lot of PH101 MCC that was tested was . On 30NOV2021 I requested the raw data associated with the studies and on 01DEC2021 I requested the referenced work request, WR-38162. I observed from the raw data documented on laboratory notebooks G4578 and G4582 (Exhibit 17 pages 2-4) that testing was completed by two analysts on 19FEB2021 rather than over a period. I also noted that the testing included sample results for each analyst rather than the sample results listed in VR-2021-000005. I verified that the 20 data entries from the notebooks otherwise matched those referenced in VR-2021-000005 for PH101 MCC Sample 2. On 08DEC2021 Ms. McDermitt stated she was unable to locate WR-38162 which detailed the testing instructions to the quality control technicians. I showed Ms. McDermitt the discrepancies between the raw data provided and the statements made in Validation Report VR-2021-000005. On 17DEC2021 Ms. McDermitt confirmed she was unable to provide records to resolve the raw data discrepancy between the laboratory notebooks and VR-2021-000005. Additionally, she confirmed she unable to provide all the raw data associated with VR-2021-000005, such as the raw data from the testing performed in the Cork Quality Control Laboratory.
A retrospective correlation study was performed using conductivity data obtained from composite and package samples for PH 101, PH102 and PH102 MCC. The study compared the conductivity results obtained when using the new non-compendial method (b)(4), the prior non-compendial method (b)(4) and the current compendial method (NF). The primary difference between the three methods is sample preparation. The analysis between the NF and (b)(4) included (b)(4) samples, between NF and (b)(4) included (b)(4) samples and between (b)(4) and (b)(4) included (b)(4) samples. The compendial (NF) specification for MCC conductivity is 75 us/cm. The firm’s specification for the (b)(4) method had been set to (b)(4) and the (b)(4) method specification was set to (b)(4) based on the bias observed through analysis. See current process specifications for MCC PH101 (Exhibit 22).

Media Preparation and Growth Promotion

The firm’s Microbiology Technicians primarily utilize microbial growth media prepared in-house for testing activities such as finished product testing for microbial enumeration and specified microorganisms. Media is prepared according to method (b)(4) entitled, “(b)(4)”, Revision 1, effective date 05MAY2020 and the preparation is recorded on the In-House Media Preparation Worksheet (Exhibit 27 pages 1-6). Per method (b)(4) entitled, “(b)(4)”, Revision 1, effective date 04MAY2020 (Exhibit 27 pages 7-12) each lot of media, prepared in-house or commercially prepared, is required to be tested for growth promotion and sterility. Method (b)(4) outlines the testing and documentation required for media usage. According to the scope of method (b)(4), all media QC is performed off-site at a contract laboratory. The report generated by the contract laboratory is sent back to the firm and media is not released for use until the vendor analysis is completed (See Objectionable Conditions Item 7B). Ms. McDermitt stated that growth promotion testing is performed off-site, and that the sterility testing of the media is executed by the firm’s Microbiology Technicians.

Documentation of QC Laboratory Product Testing

Product testing using microbiological methods is documented on both forms and in the firm’s Laboratory Management System (LIMS), while data from product testing using (b)(4) methods is documented in the LIMS (See Objectionable Conditions Item 7A&7C). Procedure PR-NWK-0012-002 (8692), entitled “General LIMS Worksheet Information”, Revision 1, effective date 11MAR2021 (Exhibit 1 pages 7-10) was modified, per Process Change 11338 (Exhibit 8), to include the requirement to print out the LIMS worksheet for composite product samples to manually enter the raw data for analytical product testing in addition to LIMS entry. Per Ms. McDermitt, laboratory notebooks are not used in the quality control laboratory to document routine product testing and the firm’s equipment does not directly interface with LIMS or provide printouts.

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RECALL
(KLC)

RES 88617- Avicel RC591 NF Lot #2173766940 OOS TAMC

On 18NOV2021 Mr. Matthew Davidson, Plant Manager and Ms. Patricia McDermitt, Quality Manager provided an overview of the investigation summary reports dated 02NOV2021 (Exhibit 33) for the Total Aerobic Microbial Count (TAMC) out-of-specification (OOS) and distribution error of Avicel RC591 NF Lot # 2173766940 drum #151. On 27AUG2021 the firm issued a recall for one drum of Avicel RC591 NF (Microcrystalline Cellulose and Carboxymethylcellulose Sodium NF) Lot # 2173766940 which was manufactured on 07SEP2020. The customer was notified that drum #151 had not passed the firm’s internal specifications for TAMC, but due to a systems failure, the firm’s third-party warehouse shipped the drum on 30OCT2020. Mr. Davidson stated that further information would be provided by IFF personnel not present onsite.

On 19NOV2021 the following personnel were available via a phone conference to provide additional context to the Avicel RC591 NF recall: Ann Gulau-Quality Manager, William Burgoon-Distribution Manager, Priscilla Sager Zawislak-Associate EH&S Regulatory Manager, Logisti Leader, Kieran O’Dwyer-Quality Leader Pharma Solutions Business, and Jennifer Laracy-Global Director QMS and CI. Information provided on the phone call included: the firm contacted the customer immediately on 27AUG2021 to inform them of the inadvertent shipment, the customer indicated to the firm that the shipment was consumed in manufacturing, and there was no product remaining to return. Additionally, Mr. O’Dwyer stated the customer used the Avicel RC591 to manufacture children’s Acetaminophen oral suspension and nasal spray.

Ms. McDermitt stated that an impact assessment had been performed but was not formally documented. Mr. Davidson elaborated that while evaluating MCC material involved in the firm’s recall for out-of-specification (OOS) conductivity, with their third-party warehouse, that it was determined MCC PH 200 NF lot 2173728724 drums # 981-1020 were to be scrapped due to a failure for presence of coliforms but were instead shipped for distribution on 05OCT2020. When accessing the error if there had been any similar occurrences, it was determined that Avicel RC591 Lot 2173766940 drum #151 was also distributed. Mr. Davidson stated that the physical relabeling of non-conforming product and scrapping of product is performed at the third-party warehouse.

Per Ms. McDermitt, MCC PH 200 NF lot 2173728724 drums were distributed to customers in and that the appropriate authorities had been notified. The customers who received MCC PH 200 NF lot 2173728724 drums included the following: and . Ms. McDermitt provided a copy of the communication (Exhibit 37), stated that the document was not written in the English language and later confirmed she did not have available a version translated in English to provide.
I was provided and reviewed the following procedures:

- PR-NWK-0000-028 (8578) entitled, “Control of Non-conforming Product”, Revision 1, effective date 22JAN2021 (Exhibit 28 page 21).
- PR-NWK-0000-043 (8975) entitled, “Finished Product Quality Labeling”, Revision 2, effective date 24SEP2021 (Exhibit 28 pages 23-29).

I commented that the procedures had lacked clear instructions on controlling non-conforming material for all scenarios that are encountered, such as product without non-pharmaceutical purposes, and/or are to be scrapped. Ms. McDermitt acknowledged my comment.

I reviewed the batch records for Avicel RC591 NF Lot # 2173766940 and MCC PH 200 NF Lot # 2173228724. Email communications were included in the batch records for lot 2173766940 (Exhibit 32 pages 11-12) and 2173228724 (Exhibit 3 pages 91-93) associated with requests to scrap the non-conforming material containers so the lots could be released. I did not observe additional supporting documentation included in the batch records for Lot 2173228724 and Lot 2173766940 that verified that appropriate actions had been taken for the material by the third-party warehouse prior to batch release.

On 22NOV2021 I was provided with DEV-06273 (Exhibit 39, pages 1-7), CAPA-00713 (Exhibit 39, pages 9-24) for Avicel RC591 NF Lot # 2173766940 with the associated action items, AI-03618 through AI-03629 (Exhibit 39, pages 25-47), and the investigation summary reports for MCC PH 200 NF lot 2173728724 (Exhibit 31). I read the firm’s investigation records for the distribution error of MCC PH 200 NF Lot # 2173228724 and Avicel RC591 NF Lot # 2173766940. Root causes concluded by the firm included both third-party warehouse personnel and IFF personnel deviating from documented procedures. The firm concluded that the third-party warehouse personnel did not respond appropriately to the firm’s requests to identify, segregate, and dispose of material per procedure. Additionally, the firm concluded IFF personnel did not follow internal procedures to further investigate inventory count discrepancies and shipment error notifications for restricted materials. I reviewed the firm’s action items without comment.

I was provided procedures for the firm (Exhibit 36), Scope of Work (SOW) dated 09JUL2020 (Exhibit 35), and records of the firm’s last audits of performed in 2018 and 2021 (Exhibit 34). I reviewed following work instructions:

- QUA-050 entitled, “Relabel Process” Version 005, date 10DEC2020 (Exhibit 36 pages 1-6).
- QUA-001 entitled, “Scrap Process” Version 007, date 16OCT2020 (Exhibit 36 pages 5-7).
- QUA-023 entitled, “Control of Nonconforming Product”, Version 007, date 31AUG2021 (Exhibit 34 pages 9-12).
I noted that procedure QUA-023 had been modified to include documented verification of actions.

**OBJECTIONABLE CONDITIONS AND MANAGEMENT’S RESPONSE**

**Observations listed on form FDA 483**

**Item 1 (CDZ)**

Changes to established procedures were not reviewed to evaluate impact on product quality.

Specifically, your firm discontinued review of data from [b](4) 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).

**Supporting Evidence and Relevance:**

According to [b] (6) [4], Process Development Engineer, the Avicel manufacturing process was validated in 2001. The validation was performed in two stages, [b](4) [4]. The [b](4) [4] stage is common to all grades of Avicel whereas the validation of the drying process was done based on particle size(grade).

<table>
<thead>
<tr>
<th>Validation Document</th>
<th>Document Number</th>
<th>Approval Date</th>
<th>Exhibit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avicel PH Grade Process Validation</td>
<td>PV01007N</td>
<td>08/31/2001</td>
<td>42</td>
</tr>
<tr>
<td>Process Validation Final Report - <a href="4">b</a></td>
<td>PV0006N</td>
<td>10/12/2001</td>
<td>43</td>
</tr>
<tr>
<td>Avicel PH 101 Drying, Storage and Conveying Process Validation</td>
<td>PV01008N</td>
<td>09/17/2001</td>
<td>44</td>
</tr>
<tr>
<td>Avicel PH 102 Drying, Storage and Conveying Process Validation</td>
<td>PV01009N</td>
<td>09/20/2001</td>
<td>46</td>
</tr>
<tr>
<td>Avicel PH 102 Drying, Storage and Conveying Process Validation – Final Report</td>
<td>PV01009N</td>
<td>10/12/2001</td>
<td>47</td>
</tr>
</tbody>
</table>
During the process validation conductivity meters measured the in-process material conductivity during the stage. Stated that the validations performed on the Drying, Storage and Conveying processes were reliant on the in-process conductivity controls. Stated that the conductivity meters were removed in approximately 2011. Mr. Davidson confirmed that no change control was authored to evaluate the effect of the discontinuation of the monitoring of the conductivity on the process.

The process validation for the process lists the conductivity meter as a “Critical Process Instrument”. Firm procedure PR-NWK-0012-001, Management of Change (Exhibit 50) requires initiation of the MOC process for equipment changes other than “replacement-in-kind”. Mr. Davidson confirmed that no documentation was generated to evaluate the impact of the removal of the conductivity meters on the process.

Discussion with Management:
Firm management indicated they understood and intended to respond in writing.

Item 2(CDZ)

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.

Supporting Evidence and Relevance:
On 04/01/2020 the firm received Complaint #00227770 (Exhibit 51) from a customer regarding incoming testing of Avicel PH-102 NF Batch P220833969 failing to meet specifications for conductivity. Ms. McDermitt stated that this was the first complaint regarding conductivity since 01/29/2018. The firm then received 3 subsequent complaints from customers regarding finished product failing to meet incoming conductivity specifications:
According to the investigation reports retain samples for all batches associated with the complaints were tested using the same equipment used in release testing. Ms. McDermitt confirmed that the retains were not subject to testing by a second conductivity meter. All lots were found to have met specification and according to Ms. McDermitt the complaints were classified as “unverified”. Investigations into complaints were performed using the Complaint Investigation – Check List (Exhibit 55 Page 9). The checklist contains a section for “Equipment Inspection”, the associated procedure gives no instructions or criteria for performing this inspection. The investigations associated with the above complaints used this section to record what equipment line was used.

Ms. McDermitt stated that the firm conducts monthly complaint trending meetings. The conductivity complaints for lots P220833969 and P220834000 were not included in the trending meetings for April 2020 (Exhibit 56), May 2020 (Exhibit 57), June 2020 (Exhibit 58) or July 2020 (Exhibit 59). She stated that the complaints were not trended at the meetings because they were “unverified”.

Discussion with Management:
I stated that without guidelines on how to perform investigations into complaints it wouldn’t be possible to bracket the problem. The conductivity meter, which later proved to be the source of the discrepancy was never challenged despite multiple third-party complaints regarding conductivity. Firm management indicated they understood and intended to respond in writing.

Item 3(CDZ)

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.

Supporting Evidence and Relevance:
Firm procedure PR-NWK-0000-033, Out-of-Specification Laboratory Results Investigation (Exhibit 60) specifies that the analyst should complete and investigation report when unexplained results are
obtained. The investigation report (Exhibit 60, page 5) is a checklist that is completed by the original analyst; it does not require a narrative explanation if the result is validated when no assignable cause can be found. Ms. McDermitt stated that the QC Lead and QA Reviewer do not conduct interviews or examine records, their signatures on the investigation report only serve to confirm that the report was completed.

Mr. Davidson stated that OOS results that fall within food-grade specifications can be downgraded using PR-NWK-000-030, Retest and(b)(4) Procedure (Exhibit 61). He further stated that there is not a large discrepancy in value between pharmaceutical and food-grade products.

A review of the following OOS results revealed that all investigations were performed by the initial analyst. There was no retesting of the sample and no examination of analyst technique or training:

<table>
<thead>
<tr>
<th>Lot Number</th>
<th>Product</th>
<th>Specification</th>
<th>Conclusion</th>
<th>Exhibit</th>
</tr>
</thead>
<tbody>
<tr>
<td>2173755142</td>
<td>Avicel PH-101</td>
<td>Conductivity</td>
<td>Assignable Cause Not Found</td>
<td>62</td>
</tr>
<tr>
<td>2173797700</td>
<td>Avicel PH-102</td>
<td>Fibers</td>
<td>Assignable Cause Not Found</td>
<td>63</td>
</tr>
<tr>
<td></td>
<td></td>
<td>*Not signed by QC Lead or QA Reviewer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2173812851</td>
<td>Avicel PH-102</td>
<td>D90</td>
<td>Assignable Cause Not Found</td>
<td>64</td>
</tr>
<tr>
<td>2173821020</td>
<td>Avicel PH-102</td>
<td>D90 and Conductivity</td>
<td>Assignable Cause Not Found</td>
<td>65</td>
</tr>
<tr>
<td>P120834017</td>
<td>Avicel PH-101</td>
<td>Conductivity</td>
<td>Assignable Cause Not Found</td>
<td>66</td>
</tr>
</tbody>
</table>

Discussion with Management:

I stated that the Investigation Report completed by the analyst would not be able to determine if there were an equipment error, analyst error or training gap. Firm management indicated they understood and intended to respond in writing.

Item 4(CDZ)

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.

Supporting Evidence and Relevance:
According to Ms. McDermitt, firm procedure PR-NWK-0000-006, *Product Recall and Mock Recall Procedure (Exhibit 67)* is used to determine the necessity for a recall. The procedure specifies that recalls would occur in the event of potential health hazards or violations of the law. The procedure does not define these terms; Ms. McDermitt confirmed that there is no other firm procedure that defines them or directs personnel when to order recalls of distributed products.

Discussion with Management:
Firm management indicated they understood and intended to respond in writing.

**Item 5(CDZ)**
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) Conductivity Meter Model (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 (b)(4) and (b)(4) 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.

Supporting Evidence and Relevance:
On 11/20/2020 DEV-04008 (Exhibit 68) was initiated to address poor response from the (b)(4) conductivity meter used in testing MCC products. The probe was cleaned and began returning readings up to (b)(4) higher than before it was cleaned. The investigation into the meter did not expand to related batches. Ms. McDermitt stated that the batches released immediately prior to the deviation initiation (Avicel PH-200 Lot 2173802516 (Exhibit 69) and Avicel PH-101 Lot 2173811666 (Exhibit 70) were not retested using the cleaned meter. Both lots were within (b)(4) of the (b)(4) release specification for conductivity. PR-NWK-0000-026, *Quality Incident Reporting (Exhibit 71)* requires the investigator to assess if other material could be affected by the deviation.

Discussion with Management:
Firm management indicated they understood and intended to respond in writing.
Item 6(KLC)

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.

Supporting Evidence and Relevance:
I reviewed procedure PR-NWK-0000-016 (8969) “Finished Product Release”, Revision 1, Effective 24AUG2021 (Exhibit 1 pages 1-5). I also reviewed batch records for lots of MCC that the firm produced in 2020 (Exhibit 3) and in 2021 (Exhibit 4) including the Shift Supervisor Logs and Maintenance Report Logs (Exhibit 5 and Exhibit 6) associated with each batch record. The batch records included the following lots: 2173966542, 2174023886, 2174023890, 2174010634, 2174010626, 2174021336, 2174021338, 2173228724, 2173762248, P120834080, P220833969, P120834253. The 2020 MCC batch records I observed were associated with a customer complaint for conductivity (Exhibit 25) or/and had been determined to have been impacted by atypical process conditions resulting in out-of-specification conductivity levels that was not detected until after distribution.

I observed that procedure PR-NWK-0000-016 does not require Quality Assurance personnel to review all relevant batch production records and the batch records did not include complete production information. Specifically, that the following were not required to be reviewed by Quality Assurance during product release and were not present in the batch records:

- Records, such as audit trails, checklists, or forms, documenting the performance or supervision of significant steps in the production process or adjustments to process parameters, in particular critical parameters.
- Production process trends, from quality indicating sources such as reactors, and, confirming critical parameters remained in a state of control during the production of each batch.

Additionally, PR-NWK-0000-016 states to review maintenance and supervisor logs for atypical operations but does not clearly define what would be considered as an atypical operation. Per Ms. McDermitt review of the Shift Supervisor Log is focused on the general comments and downtime comments each day, however there are no formally defined criteria required to be flagged as atypical or requiring further evaluation by Quality Assurance.

Mr. Davidson stated the production process is maintained and monitored in the firm’s. Mr. Davidson confirmed that the does not have
unique operator log ins and audit trails from the \( [b](4) \) are not generated for review. Ms. McDermitt confirmed that, as part of finished product release, Quality Assurance personnel do not review the \( [b](4) \) data and other relevant production process records to confirm that the process remained in a state of control, and to identify discrepancies. Mr. Davidson stated the firm’s Process Engineers review the in-process product quality. Per Mr. Davidson the review performed by the Process Engineers includes \( [b](4) \) review in LIMS for off target parameters, \( [b](4) \) reading of shift reports, as needed review of \( [b](4) \) inspection forms, as needed review of \( [b](4) \) and reaction trends, and as needed interviews of operators. According to Mr. Davidson, the firm’s Process Engineers do not provide a summary of production in-process quality trends to Quality Assurance personnel for review during finished product release for each batch or campaign. Ms. McDermitt informed me that she was unable to provide firm procedures that formalized the responsibilities of the Process Engineers to evaluate in process product quality or records documenting the Process Engineers performance of them.

Discussion with Management:
Quality Assurance personnel should be involved in all quality related matters and review all quality related documents. Batch records should contain sufficient information relating to the production and control of each batch so Quality Assurance personnel can make informed decisions and identify discrepancies during operations prior to product release.

Firm management indicated they understood and intended to respond in writing.

**Item 7(KLC)**
Laboratory control records do not include complete data.

Specifically,

A. Laboratory records do not include a second employee verifying the documentation of the data for product testing, used for release determinations (composite and packaged samples), showing that the original entries on the records have been reviewed for accuracy, completeness, and compliance with established standards.

B. 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.

C. 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.
Supporting Evidence and Relevance:
On 19NOV2021 Investigator Zagata, Investigator Akbar and I conducted a walkthrough of the Quality Control Laboratory. During the walkthrough, and subsequent review of procedures and additional records, I observed that the laboratory testing records did not include a second employee verifying the data. Additionally, each of laboratory test records did not include complete documentation showing sample preparation was in conformance with test requirements for all tests performed on each lot. Specifically, the laboratory records did not include information or a reference to pertaining to all crucial reagents and equipment used, and weight of sample measured.

LIMS microbiology laboratory records (Exhibit 15 page 59) and LIMS analytical records were observed without a second employee verification. The data entered on Microbiological Test Results form and printed chemical composite result worksheets in the batch records (Exhibit 4) were not verified for accuracy and compliance, but only completeness. Complete sample preparation data including reagents, equipment and sample weight were not present on the electronic and paper records for all tests including but not limited to microbiological testing.

There are no procedural requirements for second employee verification of the data or documentation of complete sample preparation in the following firm procedures and methods:

- Analytical Test Methods (Exhibit 10).
- Microbiological Test Methods (Exhibit 9).
- PR-NWK-0012-003 entitled, “QC Chemistry Data Entry in LIMS”, Revision 6, effective date 14MAY2018 (Exhibit 1 pages 23-30).
- (b)(4) entitled, “(b)(4) of Microbiology Test Results”, Revision 1, effective date 06MAY2020 (Exhibit 1 pages 13-17).
- PR-NWK-0012-004 entitled, “Microbiology Laboratory Worksheet Data Entry”, Revision 4, effective date 14MAY2018 (Exhibit 1 pages 11-12).

Ms. McDermitt confirmed it was not the practice to utilize second employee signatures or to record all sample preparation data for all tests on each product sample type, specifically microbiological and packaging product testing. Additionally, Ms. McDermitt stated that all changes in LIMS require a comment and the records were reviewed during product release. When reviewing laboratory testing records in the LIMS I observed modifications made without comment, modifications that occurred after the product had been distributed and modifications that were made without second employee verifications that would confirm the accuracy of the change.

On 30NOV2021 and 01DEC2021 I observed, with (b) (6), QA Specialist, the LIMS composite sample and packaging sample records for the following MCC lots: 2173966542, 2173228724, 2173762248, P120834080, P220833969, P120834253 (Exhibit 3). Procedure PR-
NWK-0012-002 Section 4.4.2 (Exhibit 1 pages 7-10) states that test results that have been modified will appear in a different color and there will be an “*” in the first column for that sample.

I examined amended records history of the change and comments sections. I observed modifications to the pH and conductivity entries for a composite sample for MCC lot P120834253, which had been signed for batch release on 30APR2020, where the original result on 21APR2020 was changed on 23APR2020 by a different QC Technician (Exhibit 15 pages 6-7). Both results appear to be passing, and the history reason states, “Performed Retest (See Comment)”. However, the comment section was empty. (b) (6) did not find an associated investigation opened in relation to the pH and conductivity of the sample tested. Additionally, he was unable to determine why the change occurred. (b) (6) confirmed that there was not a method to verify that the Quality Assurance personnel performing product release reviews the history and comments for each line item with an “*” next to it.

I observed modifications where results were adjusted, some from failing to passing, with the comments section stating wrong entered or a similar comment without a second employee verification (Exhibit 15 pages 1-5, 10-18, 23-26, 29-33, 37-43). (b) (6) commented that the first entries were likely inaccurate because they were so high. I observed several modifications to the conductivity test data entries originally conducted in 2020 for finished product packaging samples (Exhibit 15 pages 19-22, 27). (b) (6) stated that early on the firm’s investigation into customer reported out-of-specification (OOS) conductivity results and a fouled conductivity meter that retests were performed using a new meter which confirmed the OOS results. These retests occurred in early 2021 and the records with the original passing results were modified in the LIMS with the failing results from the retests. However, a decision was made to change them back in the LIMS to what was originally recorded.

I noted that even though I was examining LIMS records for batches produced and tested in 2020, that changes to procedures and LIMS worksheets in 2021 were present for some of these records. Method (b)(4) (7827) entitled, “Avicel MCC, pH and Conductance, USP-NF and EP” Revision 2 effective 23MAR21 (Exhibit 23 page 1) included a new step to measure the conductivity of “*” or and subtract that measurement from the conductivity value of the test solution. However, a LIMS record for conductivity on MCC lot 2173728724 (Exhibit 15 page 61), with batch release approval on 07AUG2020, had empty fields which included the conductivity measurement of the water even though lot 2173728724 would not have been tested against the revision of the method requiring that data. The records appeared as though information was incomplete and tested incorrectly. (b) (6) did not have an explanation as to why samples observed in the worksheets had been modified to include the additional fields.

Furthermore, I observed in the LIMS that samples within the worksheets were set to “M” for “moved/ready to release”, instead of “R” for released (Exhibit 15 pages 13-15). The finished
products had been dispositioned to release and distributed, however the laboratory testing data on these records for packaging and composite samples were able to be further modified. Per Ms. McDermitt, in the “M” stage the records could be modified and only Quality Assurance personnel had access to move from stage “R” back to “M”. Ms. McDermitt provided a list of user access of personnel and permissions for LIMS (Exhibit 14). She later stated that occasionally and LIMS interface would not communicate correctly, and the LIMS samples would remain in the “M” stage.

7B

On 19NOV2021 Investigator Zagata, Investigator Akbar and I conducted a walkthrough of the Microbiology Laboratory. During the walkthrough, I observed media being used for routine microbiological product testing prior to quality control release. The media was not documented as acceptable for use on the firm’s forms, and the contract laboratory’s reports were not present with the forms. During my subsequent review of the same records, I observed the documentation had been retrospectively filled in by the firm’s Microbiology Technician with no additional notation or justification with the entries.

I observed (b)(4) Agar (b)(4) Lot (b)(4) in the refrigerator and reviewed the In-House Media Preparation Worksheet. Lot exp: 21JAN2021, had been prepared on 21OCT2021. The contract laboratory analytical report was not attached and there was not a signature or initials with date indicating the media was acceptable for use (Exhibit 13 pages 4-5). Media types and lots used for the day as well as the lot and sample numbers initially tested are documented on Negative Control Logs. (b)(4) Lot (b)(4) was documented as being used for product testing on the Negative Control Logs from 14NOV2021, 15NOV2021, and 17NOV2021 (Exhibit 13 pages 1-3). (b)(4) lot (b)(4) was documented in the Negative Control Logs for product testing on 27OCT2021 though 19NOV2021 (Exhibit 11 pages 40-65).

Similarly, I observed media lots documented on Negative Control Logs that had incomplete worksheets including, but not limited to, the following:

- (b)(4) Lot (b)(4) exp: 06FEB2022 prepared on 06NOV2021 (Exhibit 13 page 1& 6).
- (b)(4) Lot (b)(4) exp:04FEB2022 prepared on 04NOV2021 (Exhibit 13 pages 1-3, 8-9).
- (b)(4) Lot (b)(4) exp: 23DEC2021 prepared 23SEP2021 (Exhibit 13 page 1-3, 10-11).
Lot was documented for use on the Negative Control Log on 23SEP2021, the day it was prepared ([Exhibit 11 pages 23-62]) prior to being documented off test for sterility on 27SEP2021, through 19NOV2021.

Lot was documented for use on the Negative Control Log on 01OCT2021 ([Exhibit 11 page 31-62]), prior to being documented off test for sterility on 03OCT2021, through 19NOV2021.

Agar Lot exp: 15DEC2021 prepared 15SEP2021 was signed and dated as acceptable on 28SEP2021 ([Exhibit 12 pages 1-3]) which corresponded with the attached report from the contract laboratory. However, Agar Lot 21005 was documented for use on the Negative Control Log on 21SEP2021 through 19NOV2021 ([Exhibit 11 pages 21-62]).

According to the batch records for MCC PH101 Lot 2174021336 ([Exhibit 4 page 221]), sample was placed on test on 22SEP2021 in an . Between 23SEP2021 and 25SEP2021 the for MCC PH101 Lot 2174021336 was transferred to Agar for absence of and Agar for absence of . I observed that on the Negative Control Logs ([Exhibit 11 pages 23-28] the Microbiology Technicians documented Agar lot 21005 and Agar lot 21007 as being used. Agar lot 21005 exp: 15DEC2021 was used for microbiological testing of MCC PH101 Lot 2174021336 prior to the contract laboratory completing analysis and returning the report to the firm. Additionally, Agar lot 21007 was used for microbiological testing of MCC PH101 Lot 2174021336 prior to both sterility and growth promotion test completion.

Method entitled, “ Revision 1 effective date 23APR2020 ([Exhibit 1 pages 19-21]) does not require the Negative Control Log form to be reviewed when control results are negative. Release Coordinator confirmed that review of the Negative Control Logs does not include verification that the media documented for product testing has been signed off for quality release. Ms. McDermitt confirmed the Negative Control Log Forms are not verified when the microbiological records are reviewed during finished product release.

Additionally, on 23NOV2021 some of the records that I had originally observed, and Ms. McDermitt had earlier provided me copies of had been since then modified to include the contract laboratories report and the media assessment with initials and date. Lot exp 28DEC2021 the record originally did not have a quality check of acceptable and signature, however when I later observed from the record directly in the binder, provided from the Microbiology Laboratory, the media was checked as acceptable with initials and date of 09OCT2021 ([Exhibit 13 pages 17-22]). Similarly, for Lot exp 24DEC2021, the original record observed did not have a quality check of acceptable and signature or an attached report, however, when I later observed the record in the binder the report was attached, the media was checked as acceptable with initials and date of 08OCT2021([Exhibit 13 pages 12-16]). The modified records did not include a comment that
laboratory controls were not followed and documented at the time of performance or explaining the departure from procedure. Ms. McDermitt confirmed that a deviation had not yet been opened for the occurrence. The contract laboratory tested the media in question and the growth promotion results passed. However, the documented assessment that the media was determined to be acceptable prior to use in testing was not performed and records were later modified by the Microbiology Technician.

Discussion with Management:
Laboratory records should include complete data and there should be meaningful review of the records to assure accuracy and compliance in addition to completeness. Additionally, laboratory controls should be followed and documented at the time of performance. Any departures from procedures should be documented and explained contemporaneously. The integrity of the raw data and laboratory records should be maintained. Measures should be taken to prevent unwarranted modifications or deletions of records.

Firm management indicated they understood and intended to respond in writing.

**Item 8(KLC)**
Analytical methods were not adequately verified for suitability under actual conditions of use.

Specifically, your firm uses a compendial method for conductivity on composite samples of finished Microcrystalline Cellulose (MCC) and a non-compendial method for conductivity on packaged samples of finished MCC. Results from the composite samples and packaged samples are used for final disposition and release determinations. In approximately March 2021 your firm modified both your internal compendial and non-compendial methods for MCC without appropriate evaluation.

For example, your firm performed two precision conductivity studies for MCC using the compendial method and a (b)(4) on data from compendial and non-compendial methods between January and March 2021. The conductivity data evaluated did not reflect a range of values that may be obtained during routine testing.

Supporting Evidence and Relevance:
Conductivity is a product quality critical process parameter of the firm’s Microcrystalline Cellulose (MCC) (**Exhibit 2 pages 1-12**). The firm’s QC Laboratory uses a compendial method (**Exhibit 23 page 1, 5-6**) for conductivity on composite samples of finished Microcrystalline Cellulose (MCC) and a non-compendial method (**Exhibit 23 pages 3-4, 7-8**) for conductivity on packaged samples of finished MCC. Also, in-process samples of MCC are tested with the non-compendial conductivity method. The firm’s compendial and non-compendial methods conductivity had been modified earlier...
Establishment Inspection Report

Dupont Nutrition USA, Inc.
Newark DE, 19711

FEI: 3013947845
EI Start: 11/17/2021
EI End: 12/15/2021

this year as referenced in Process Change 11384 (Exhibit 21) and CAPA-00456 on 14DEC2020 (Exhibit 26).

On 17NOV2021 I requested the method validation records for Microcrystalline Cellulose (MCC) conductivity testing. Ms. McDermitt confirmed she could not provide the validation records for MCC conductivity prior to modification of methods in approximately March 2021. Additionally, she stated that these records were not available as a reference during the execution of VR-2021-000005. I was provided Validation Report VR-2021-000005 entitled, “Conductivity of Microcrystalline Cellulose”, dated 14APR2021 (Exhibit 16). I reviewed VR-2021-000005 and observed that the conductivity data evaluated in the report did not reflect a range of values that may be obtained by the firm during routine testing.

Concluded in Validation Report VR-2021-000005 was that the method has been shown to be valid over the range of [b](4). The conclusion was derived from the [b](4) from the two precision studies with a subsequent average conductivity of [b](4) and [b](4) for the two lots PH101 MCC tested. I observed conductivity test results with values below and above this range for testing MCC using compendial methods (Exhibit 24). MCC conductivity results as low as 35us/cm were recorded by the firm’s QC Laboratory using the compendial test method from (Exhibit 24 page 3). Also, MCC conductivity results as high as 119us/cm were recorded by the firm’s QC Laboratory using the compendial method (Exhibit 24 page 6). The upper and lower values were not sufficiently challenged and there were not midline values evaluated between the range that would be encountered in actual use. Additionally, concluded in the Validation Report VR-2021-000005 was that the new [b](4) is able to measure the conductivity of the MCC samples and provide results that are equivalent to the NF procedure. I observed data evaluated during the [b](4) represented results primarily within specification and did not reflect a higher range of values, that included highly failing results, when making the assessments of [b](4) and method variability.

Discussion with Management:
There should be appropriate evaluation of modified methods. The evaluation should encompass an appropriate range of values to adequately challenge the method and the values should be specific to the intended application. Firm management indicated they understood and intended to respond in writing.

REFUSALS

No refusals were encountered during the current inspection.
GENERAL DISCUSSION WITH MANAGEMENT
(CDZ)

On 12/15/21 a closeout meeting was held with the following firm personnel:

Matthew James Davidson - Plant Manager
Patricia McDermitt - Quality Manager
(b) (6) – Quality Improvement Leader
Charles Allen – Area Manager – MCC Operations

Participating via teleconference:
Kieran O’Dwyer – Quality Leader Pharma Solutions Business
Joshua Stevens - Associate Quality Manager
Ann Gulau - Quality Manager

An 8-item Form FDA-483, Inspectional Observations was issued to Matthew J. Davidson, Plant Manager. Firm management was given the opportunity to ask questions and indicated they intended to respond to the FDA-483 within 15 business days.

Additionally, a discussion item was presented for the following:

- Firm procedures are in many cases vague. Protocols often contain phrases like “employee should…” or contain responsibilities that employees should perform without an explanation of the process. Procedures such as conducting investigations or criteria to determine whether a process should be performed should be specific and detailed.

ADDITIONAL INFORMATION

EXHIBITS COLLECTED

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## Establishment Inspection Report

**Establishment Name:** Dupont Nutrition USA, Inc.  
**Address:** Newark DE, 19711  
**FEI:** 3013947845  
**EI Start:** 11/17/2021  
**EI End:** 12/15/2021

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### SIGNATURE

**Craig Zagata, Investigator**  
**Kristina L. Conroy, Investigator**  
**Sayyem H. Akbar, Investigator**