REDICA Systems

Breaking News: The First FDA Warning Letter to an Excipient Manufacturer

EXPERT COMMENTARY

WRITTEN BY

BARBARA W. UNGER
SENIOR GMP EXPERT

IDEA IN BRIEF

The FDA issued a first-of-its-kind warning letter to an excipient manufacturer. This likely opens the door to a wide-ranging set of firms that could be inspected and receive enforcement actions, with potentially serious consequences for those who purchase excipients from firms with quality failures.

For dosage form manufacturers - Ensure that your excipient suppliers are adequately qualified and that oversight, including on-site audits, is adequate. The FDA issued warning letters in the recent past for those who purchased and used materials from firms that are under a warning letter enforcement or an import alert. Use of an excipient deemed to be adulterated, as in this case, strongly suggests that a drug product made with this excipient may also be adulterated.

For excipient manufacturers - Evaluate whether your quality system has similar shortcomings that may result in FDA determining that your products are adulterated.

For the industry - The reach of this enforcement action could be extensive considering the number of dosage forms in which the excipient identified in the warning letter is a component. We will continue to follow what I'm sure will be an ongoing effort within the industry.

BACKGROUND

On December 2, 2022 the FDA issued a warning letter to DuPont Nutrition USA Inc (Newark, Delaware), based on an inspection conducted by three investigators between November 17 and December 15, 2021 (actually on-site 12 days, according to the form-483). The FDA posted the Warning Letter on its website on December 20, 2022. The Redica platform includes the Inspection record, the Warning Letter, the form-483, the EIR, and a second response to the form-483 that provides follow-up progress to their original response to the 483.

The FDA identifies the firm as an "Excipient Manufacturer" in the form-483 and in the warning letter. This is the first warning letter that identifies an excipient manufacturer

as the subject of such an enforcement action. Excipients have been mentioned in warning letters issued to dosage form manufacturers, but the shortcomings were based on the actions of the dosage form manufacturer. This includes, but is not limited to, failure to perform identity tests of incoming excipients, failure to adequately document weights of excipients added during formulation, and acceptance of excipients on a certificate of analysis only.

(Note: The EU GMP guide states that dosage form manufacturers must determine the level of GMP compliance required of their excipient manufacturers in a Guideline dated March 19, 2015, and included within Part III of the Good Manufacturing Practice guidelines. FDA has no such explicit requirement or guidance.)

Interestingly, the text of the warning letter and the deficiencies are very similar to warning letters issued to both API manufacturers and drug dosage form manufacturers. This indicates that the quality principles the FDA enforces are ubiquitous across all drug manufacturing and suppliers. These deficiencies include shortcomings in change control/management, investigations that do not adequately identify root cause(s), failure to implement CAPA(s) to prevent future problems, failures in data governance/data integrity, and inadequate analytical method validation and verification.

First-of-a-kind enforcement actions are always of interest in terms of what they tell us about the FDA's potential future enforcement in this area. Also, the text in the enforcement action provides insight into what the FDA found to be the specific objectionable activity or process so others who operate in this area may evaluate their procedures and processes. Based on this warning letter, all excipient manufacturers should evaluate their operations to determine if they have similar shortcomings. And firms that purchase excipients should ensure that oversight of their suppliers is adequate to identify similar shortcomings.

The FDA approach to supplier oversight is not new. In FY2017, FDA issued warning letters to ChemRite CoPac Inc, a contract manufacturer, and Sage Products Inc, the associated product sponsor. Recently, FDA also cited firms that used materials sourced from suppliers under import alert or were the recipient of warning letters. Similar actions could be taken here against many dosage form manufacturers when considering the broad use of this excipient and others identified in the EIR.

THE INSPECTION AND 483:

The firm submitted Drug Master File 449 to FDA to address Avicel®, a microcrystalline cellulose excipient used "…as a compression and flow aid in multiple drug product formulation." The 31-page EIR identifies this as a For Cause Inspection requested by CDER and states that the previous inspection in 2010 was classified NAI. Unfortunately, the memo from CDER requesting the inspection is not included in the EIR. FDA establishes its jurisdiction over the firm by listing eleven drug components commercialized in interstate commerce by the firm.

At the end of the inspection the FDA issued a form-483 with eight observations. Briefly, these include, with numbering as assigned by FDA:

1. Failure to adequately assess changes to procedures for their impact on product quality. This addressed a change to discontinue the review of data from conductivity meters.
2. Complaints are not adequately managed to determine root cause and identify events that may justify a product recall. Examples include OOS events for conductivity.
3. OOS investigations are performed by the original analysts and do not consider equipment or analyst errors.
4. The recall procedure does not identify conditions that necessitate a recall.
5. Not all lots that may have been impacted are included in investigations. The example addresses the conductivity meter/probe used to test product where results are used in product release.
6. Batch record review does not include all relevant records, including critical in-process parameters, to ensure the process remains in a state of control.
7. Laboratory records do not include complete data, including documentation of second-person verification and details about sample preparation. Further, FDA identified backdating of records, and failure to document data contemporaneous with its generation.
8. Analytical methods are not verified to be suitable under

conditions of use. Again, the method used as an example here is the test for conductivity.

Note that observation #7 addresses failures in fundamental expectations to ensure integrity of the data generated by the firm. The EIR provides additional information on data governance failures including "*…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*" The FDA reviewed testing records in LIMS and "*…observed modifications [made in LIMS] 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.*"

WARNING LETTER

The warning letter resulting from this inspection and DuPont Nutrition USA Inc.'s inadequate response includes five deficiencies. The warning letter was issued approximately a year after the inspection, almost twice as long as the average warning letter issuance interval for drug GMP failures. This enforcement action was likely the source of extensive discussion within FDA including legal, resulting in the lengthy delay.

FDA deems the excipient to be adulterated for two reasons: controls for manufacturing, processing, packing, or holding do not conform to CGMP, and excipients fail to conform to compendial standards for strength, quality, or purity. 21CFR 211 is not cited, but the FD&C Act and relevant U.S.C. section are cited. This is similar to how FDA warning letters to API manufacturers are managed in identifying the requirements that were not followed.

The warning letter includes five deficiencies:

1. Failure to adequately address complaints, including approximately 50 complaints for failing to meet conductivity specifications as documented in the USP. Further, it took three months to communicate with customers after opening an investigation, and actions such as recalls were not implemented until nine months after the firm became aware of the conductivity test failure.
2. Investigation into OOS events was inadequate and did not include a supervisor evaluation of the records and test data nor did it include evaluation of other potentially affected lots. Root cause was not determined, and an effective CAPA(s) was not identified.
3. Failure to verify and validate compendial and non-compendial test methods, respectively.
4. The change management process was not adequate to evaluate the potential impact on the excipient product. The firm said they did perform an evaluation, but it was not documented.
5. And last but not least, laboratory records did not include complete and accurate data, nor were activities recorded at the time they were performed.

FDA further states, "*Your quality system does not adequately ensure the accuracy and integrity of data to support the safety, effectiveness, and quality of excipient you manufacture.*" They strongly recommend a consultant with expertise in data integrity to assist in remediation that they specify in detail. FDA points the firm to the FDA OOS guidance to help in their remediation of investigations.

While not addressed in the warning letter, FDA provides additional detail in the EIR. Microbiological test results are also implicated as being OOS events that were not managed appropriately. By the time the firm notified the customer and recalled the product, it was already used in the manufacture of drug product. This raises the question of whether the drug product manufacturer conducted a recall of their drug product based on the excipient recall.

CONCLUSION

This warning letter has far-reaching implications for manufacturers of excipients and those who purchase these products. For each of the five deficiencies FDA identifies information that should be provided in response to the warning letter. This is consistent with FDA practices of the last few years where they identify specific remediation actions.

All excipient manufacturers should evaluate whether their quality system has similar shortcomings that may result in FDA determining their excipient product is adulterated. This seems to open the door to a potentially wide-ranging set of firms that could be inspected, with serious responsibilities and potential consequences for those who purchase the excipients.

Dosage form manufacturers should ensure that their excipient suppliers are adequately qualified and that oversight, including on-site audits, is adequate. Those who purchase the excipient mentioned in the warning letter (or identified by FDA in the EIR) should determine if they are provided by the firm in question and if so, what actions should be taken. FDA issued warning letters in the recent past for those who purchased and used materials from firms that are under a warning letter enforcement or an import alert. Use of an excipient deemed to be adulterated, as in this case, strongly suggests that a drug product made with this excipient is also adulterated.

The reach of this enforcement action could be extensive considering the number of dosage forms in which it is a component. We will continue to follow what I'm sure will be an ongoing effort within the industry.

ABOUT THE AUTHOR

Barbara Unger formed Unger Consulting, Inc. in December 2014 to provide GMP auditing and regulatory intelligence services to the pharmaceutical industry, including general GMP auditing and auditing and remediation in the area of data management and data integrity. Her auditing experience includes leadership of the Amgen corporate GMP audit group for APIs and quality systems. She also developed, implemented, and maintained a comprehensive GMP regulatory intelligence program for eight years at Amgen. This included surveillance, analysis, and communication of GMP related legislation, regulations, guidance, and industry compliance enforcement trends. Barbara was the first chairperson of the Rx-360 Monitoring and Reporting work group (2009 to 2014) that summarized and published relevant GMP and supply chain related laws, regulations, and guidance. She also served as the chairperson of the Midwest Discussion Group GMP-Intelligence sub-group from 2010 to 2014. Barbara was also the co-lead of the Rx-360 Data Integrity Working Group from, 2017 through 2019. She currently serves as a GMP consultant to the Redica Systems team, beginning in 2015, then known as FDAzilla.

Barbara received a bachelor's degree in chemistry from the University of Illinois at Urbana-Champaign. You can contact her at barb.unger@redica.com.

REDICA Systems

Redica Systems Analysis: DuPont Nutrition USA Inc. Warning Letter

EXPERT COMMENTARY

WRITTEN BY

JERRY CHAPMAN
SENIOR GMP QUALITY EXPERT

REDICA SYSTEMS ANALYSIS: DUPONT NUTRITION USA INC. WARNING LETTER ISSUED DECEMBER 2, 2022

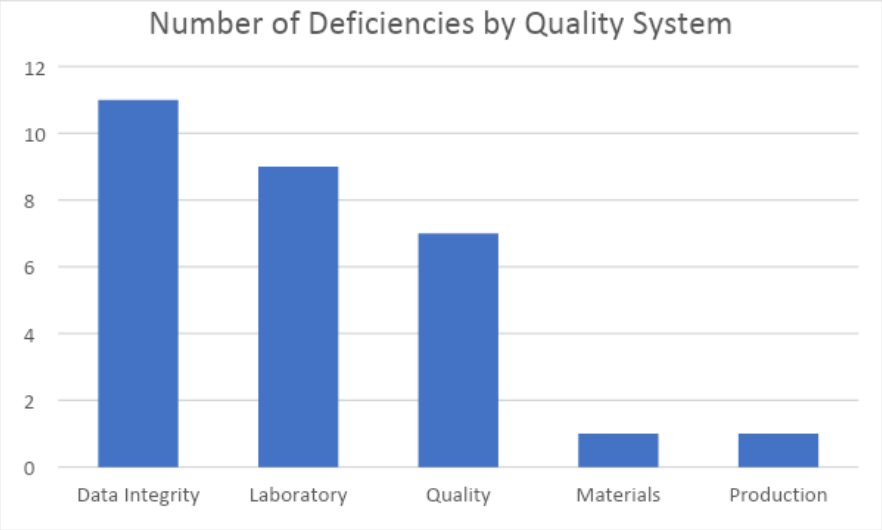
An FDA Warning Letter contains numerous sections. The key sections for this analysis are the numbered deficiencies and supporting examples. These have been evaluated by the Redica Systems expert model algorithm and the deficiencies have been mapped to the 6+1 Quality Systems (and specific aspects of those systems) and are marked by color highlighting with a mapping key in the right column. The 6+1 quality systems are: Production, Materials, Laboratory, Packaging and Labeling, Facilities and Equipment, Quality, and Data Integrity.

ABOUT QUALITY SYSTEM LABELING IN REDICA SYSTEMS

One of the big challenges for quality professionals in life sciences is getting actionable, reliable data in an efficient, structured manner. As you can see from this Warning Letter text below, there is a lot of insight to be gained once you read and thoroughly understand the entire document. For example, the fact that there are three prominent categories of deficiencies cited in this Warning Letter: Data Integrity, Laboratory, and Quality. Redica Systems ingests thousands of similar documents and tags them so that your team can easily run sophisticated analyses while saving hundreds of hours of manual labor. This is part of our Quality System Labeling capability. Redica Systems turns unstructured data from many different sources into structured data, ready for sophisticated analysis, with the Redica ID at the center.

SUMMARY OF MODEL FINDINGS:

Deficiencies were mapped to the Production, Materials, Laboratory, Quality, and Data Integrity systems, and are summarized here in order of prevalence:



- Data integrity deficiencies include issues with accuracy, data manipulation, raw data, and data not recorded contemporaneously with its acquisition
- Laboratory issues map to Out of Specification/Out of Trend (OOS/OOT) issues, general lab controls, control of impurities, and method validation
- Quality system deficiencies include issues with complaint management, change control, and deviation investigations
- Materials system deficiency is with certificates of analysis
- Production system issue maps to process performance qualification

Text of the letter and deficiencies found by quality system:

1. Your firm failed to perform adequate investigation of complaints. Your firm manufactures microcrystalline cellulose (MCC) under the brand name Avicel, which is included in Drug Master File (DMF) 449 submitted to FDA. Avicel is used as a compression and flow aid in multiple drug product formulations. Between April 2020 and June 2021, you received approximately 50 complaints related to your Avicel excipient failing to meet the conductivity specifications. The conductivity quality standard for MCC is delineated in the U.S. Pharmacopeia (USP). Failure to meet applicable USP standards also renders drugs adulterated under section 501(b) of the FD&C Act. You did not adequately evaluate these complaints. You only included retest and release data review in your initial investigation into conductivity complaints for Avicel. It was not until seven months later that you discovered your conductivity meter probe was encrusted with residue, thus giving inaccurate conductivity results. This conductivity meter was used for batch release testing and retesting as part of your complaint investigations.	Quality System I Complaint Management Data Integrity I Accurate

Your initial complaint investigation did not adequately evaluate whether your malfunctioning conductivity probe was potentially associated with these out of specification (OOS) conductivity complaints, especially when you determined that the complaints could not be verified.

Laboratory | OOS / OOT

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

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

Laboratory | OOS / OOT

Your investigations into failing test results are inadequate.

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

Quality System | Deviations/Investigations Inadequate - No Root Cause

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

Data Integrity | Accurate

Laboratory | OOS / OOT

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

Laboratory | Laboratory Controls / Impurity Control

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

Laboratory | Method Validation

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

A. You failed to verify the compendial conductivity test method and evaluate if additional verification parameters or validation were required due to changes in sample preparation.

For example:

- You failed to have an approved method verification protocol with pre-established requirements for your most current (April 13, 2021) test method report. You were also unable to locate the testing instructions for your precision study. — Data Integrity | Raw Data
- Your compendial method verification failed to evaluate accuracy of the test method.
- You lacked scientific rationale to support the range evaluated during the method verification ((b)(4) of the specification limit).
- You lacked adequate scientific justification to identify an anomalous result obtained during your precision study as an "outlier" and to exclude it from the study.
- Review of your raw data compared to your report indicated discrepancies in the number of samples and the timing of testing.

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

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

C. You inappropriately used composite sampling.

While you utilized your non-compendial "(b)(4)" for individual packaged samples, the certificate of analysis included the result of the composite sample. — Materials | Material Sampling and Testing / Certificate of Analysis

A review of the data indicated passing composite sample results comprised of samples which included individual failing packaging samples. The use of composite sampling may have allowed the release of OOS Avicel to the market. Additionally, your practice of composite sampling is concerning considering your non-compendial "(b)(4)" provided inaccurate results and you were using composite samples inappropriately for release testing. — Data Integrity | Accurate

You lacked an adequate scientific rationale for the use of compendial test methods for composite samples and non-compendial test methods for in-process and packaged samples. — Quality System | Change Control | General

4. Your firm failed to have an adequate change management program to evaluate and approve changes that may impact the quality of the excipient. — Production | Process Validation Inadequate or Missing

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

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

During the inspection, your laboratory personnel backdated the approval section of an in-house microbiological media preparation worksheet after the media had been used. In addition, your microbiology laboratory personnel were observed using unreleased microbiological growth media plates during drug testing. Your personnel improperly retested pH, conductivity, loss on drying, and particle size samples. We observed failing results changed to passing based on retest results. You were unable to provide adequate investigations or justification associated with the retests. Your sample testing records are incomplete because they do not include information about sample weight, and a reference to reagents and instruments used. Without complete, timely, and accurate testing records, you cannot adequately evaluate the quality of your excipient, make appropriate batch release decisions, or fully understand the potential impact of poor manufacturing practices on the quality of your excipient. **Data Integrity Remediation**	Data Integrity I Data Manipulation
Your quality system does not adequately ensure the accuracy and integrity of data to support the safety, effectiveness, and quality of the excipient you manufacture. You may find principles outlined in the FDA's data integrity guidance helpful as you consider remediating this issue, see Data Integrity and Compliance With Drug CGMP at https://www.fda.gov/media/119267/download.	Data Integrity I Accurate

REDICA Systems

Event Chain - DuPont Nutrition

CDER memo	FDA on-site Inspection	Form 483 / VAI	Establishment Inspection Report	483 Response & Additional Response	Warning Letter	...
9/7/2021	12/15/2021	12/15/2021	1/14/22	1/12/2022 & 2/15/2022	12/02/2022	

Pilot program for excipients: Issues related to formulation and stability

Inspection
Reason: for-cause

Inspection days: 12

Lead Investigator: Craig Zagata

Investigators: 3

Form 483

Observations: 8

EIR

Pages: 31

Form 483R

Inspection
Outcome:
Warning Letter

Warning Letter

Deficiencies: 5

Redica Comment

For-cause inspection usually due to FDA information on public health concern

3 Investigators for 12 days is also above normal

Potential Critical Observations:

- Data Integrity: Accuracy & Original Data
- Quality System: Failure to Investigate
- Quality System: Complaint Management
- Laboratory: Controls & Method Validation

For Cause inspection initiated due to numerous unaddressed customer OOS complaints over the course of 8 months

Limited Product Recalls specifically addressed

Initial company response lacked expected detail and scientific reasoning to add observations fully

Company had to submit an additional response

cGMP Consultant recommended, especially for Data Integrity remediation

A first-of-its-kind Warning Letter to an excipient Manufacturer

Read more