REDICA Systems

First FDA Warning Letter to Excipient Manufacturer Provides Lessons

EXPERT ARTICLE

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In December 2022, FDA issued a Warning Letter to DuPont Nutrition USA Inc., an excipient manufacturer. It was the first Warning Letter to be issued to an excipient-only manufacturer. This letter sends a signal from the agency with implications for both users and manufacturers of excipients. Why is this important to understand and pay attention to?

WHAT IS AN EXCIPIENT?

According to the *U.S. Pharmacopeia*, excipients are "often referred to as 'inactive ingredients' because, in drugs, they comprise of everything except the active pharmaceutical ingredients (APIs). Excipient functions range from helping to guarantee the stability and bioavailability of the API to the drug product's manufacturability to its texture and taste. Excipients are a major component of almost all drugs, as well as foods, cosmetics, and dietary supplements."

It is important to note that "almost all" drugs contain excipients. And since an issue with an excipient could indicate a problem with the drug it is used in, drug manufacturers must be aware when problems arise with the excipients they use in their finished products. The excipient targeted in the Dupont inspection is widely used in numerous drug products.

INSPECTION AUTHORITY AND FREQUENCY

FDA has an active and formal inspection program for drug manufacturers. Inspections are regularly performed at sites that manufacture APIs and the finished dosage form (FDF) products they are used in, i.e., the products that are sold and administered to patients, such as pills and capsules.

FDA has the authority to inspect drug manufacturing under the FD&C Act of 1938 and the numerous amendments added to it

since by the U.S. Congress. It publishes regulations in the *U.S. Code of Federal Regulations* (CFR), which have the force of law, and guidance documents on its website to help the industry understand the agency's current thinking regarding Good Manufacturing Practices (GMPs).

Excipients, however, are not drugs but drug components and as such, are not subject to the CFR, which is specific to finished drug products. However, they are subject to the FD&C Act and are under FDA jurisdiction when they are transported via interstate commerce. Inspections of excipient manufacturers, unlike the regular surveillance inspections of drug manufacturers, are rare – the Redica Systems platform shows only 12 inspections of excipient manufacturers since 2000.

WHAT PROMPTED FDA TO INSPECT DUPONT NUTRITION?

FDA conducts regular inspections, called surveillance inspections, of drug companies on a periodic basis, and "For Cause" inspections when, as the name implies, the agency has reason to believe there are public health concerns at a facility that may require more timely agency action.

When FDA investigators conduct an inspection, an Establishment Inspection Report (EIR) is generated, which details the inspection. At the end of an inspection, if potential deficiencies are observed, they are detailed in an FDA Form 483. After the company has had a chance to respond and the agency has evaluated the response, if it deems the response lacking a Warning letter may be issued.

Here is a timeline showing the sequence of events that led to the Dupont Warning Letter:

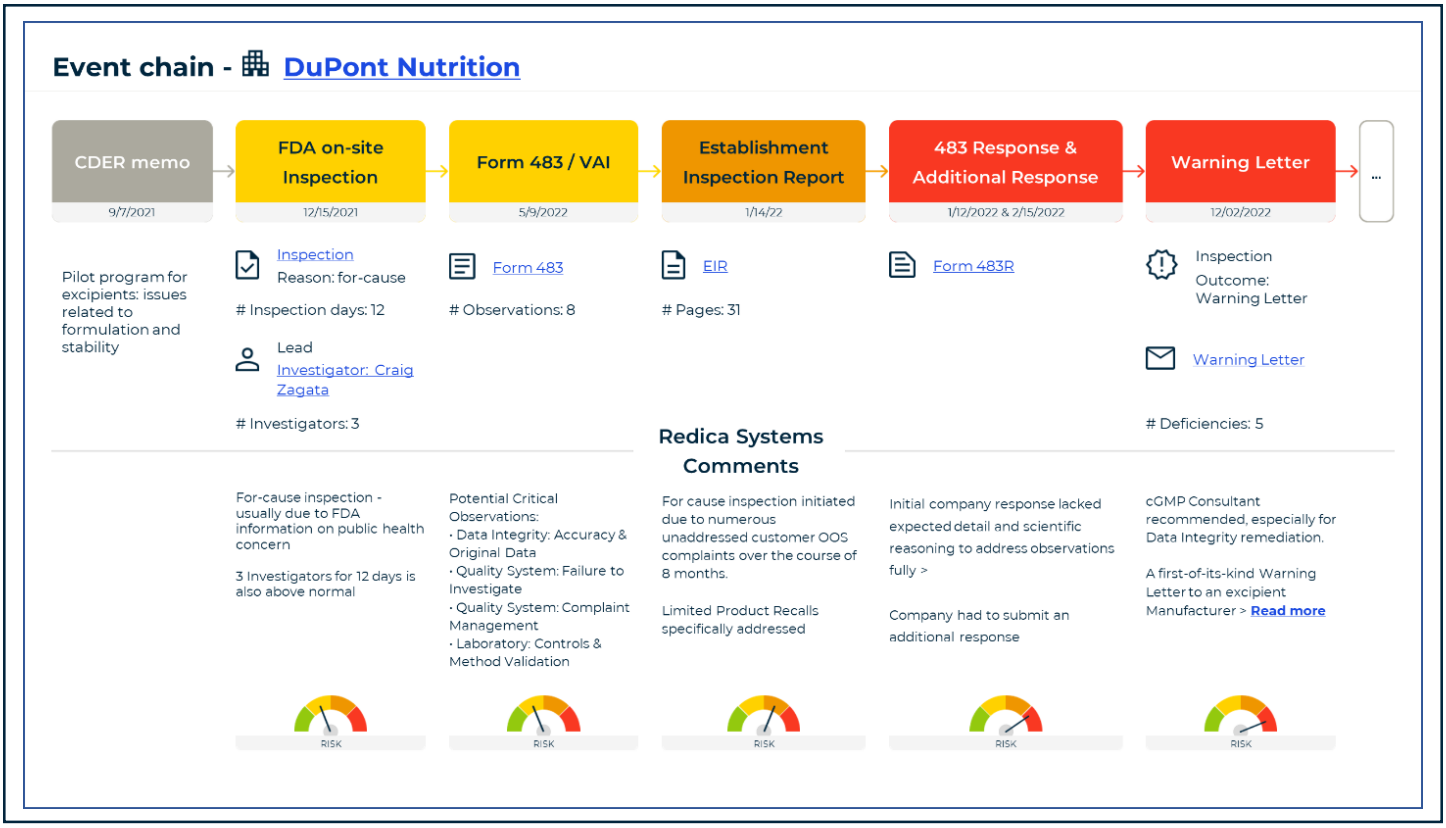

FIGURE 1 | EVENT CHAIN FOR DUPONT NUTRITION

In the case of Dupont Nutrition's November-December 2021 inspection, the EIR, the resulting 483, the company's 483 response, and the subsequent December 2022 Warning Letter are all available on the Redica Systems platform.

The 31-page EIR identifies the DuPont inspection as a "For Cause Inspection" requested by the FDA Center for Drug Evaluation and Research (CDER) and references a memo from CDER requesting the inspection. The CDER memo is not included as part of the EIR but has been requested by Redica Systems through the Freedom of Information Act (FOIA).

Although the specific reason for the inspection is not detailed, examination of the 483 provides strong clues. An FDA Form 483 generally lists the observations the investigators find in order of concern, with the most concerning first.

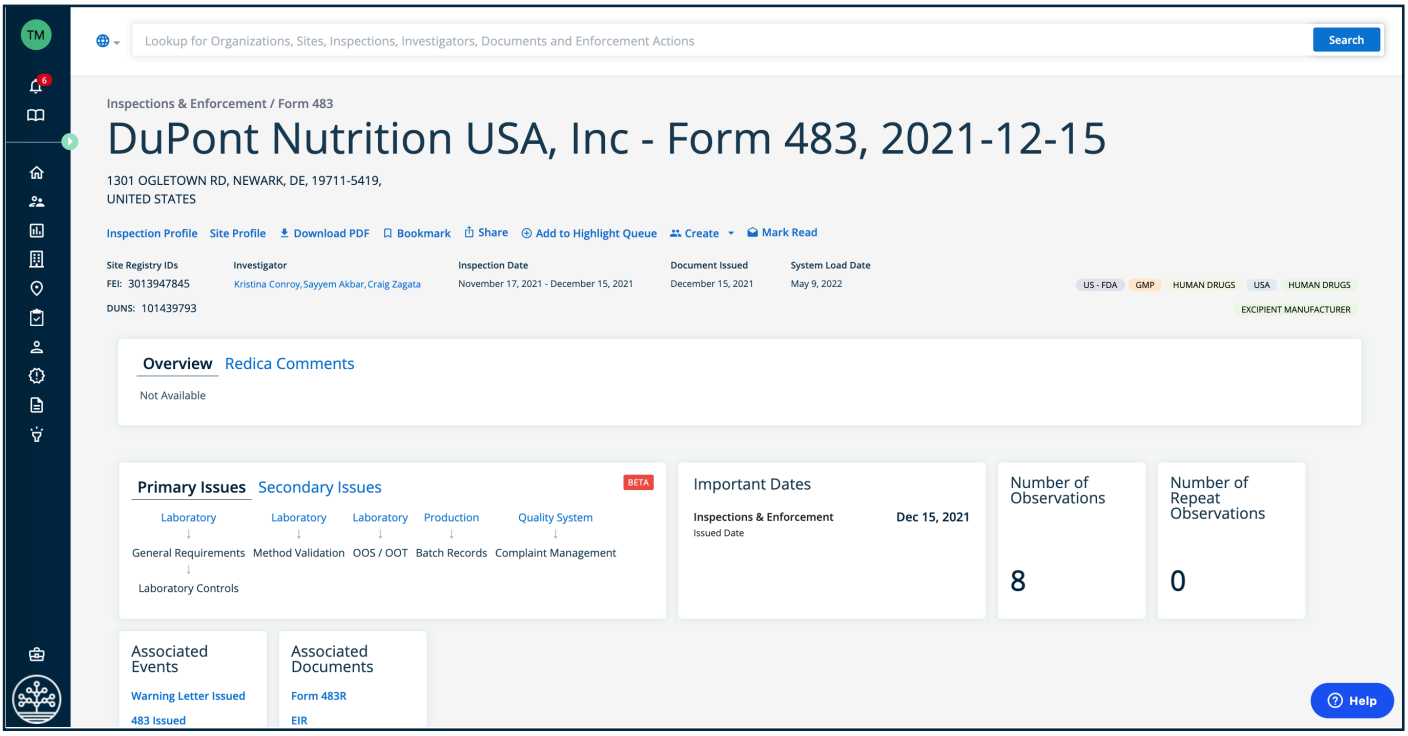

FIGURE 2 | DUPONT 483 IN REDICA SYSTEMS PLATFORM

In the DuPont 483, the first observation points to changes to procedures that were not reviewed for their impact to product quality – specifically, discontinuing evaluation of measurement data of a property of the excipient known as "conductivity."

The second observation states: "Complaints are not adequately handled to determine the root cause and assure it does not recur and to detect product quality events that may warrant a recall…. For example, between April 2020 and May 2020, four customer complaints were received for out-of-specification (OOS) conductivity of Microcrystalline Cellulose (MCC)..."

Taken together, these show that the company received complaints from customers for the MCC product that failed to meet the specification for conductivity and that it may have resulted from the firm discontinuing review of conductivity data. It is not a stretch to speculate that the "For Cause Inspection" resulted from FDA becoming aware of customer complaints regarding DuPont's MCC product. And according to the second observation, FDA is concerned that the company may not have systems in place to detect issues that warrant a product recall. The MCC excipient is widely used by numerous companies in drug formulations.

WHAT DID FDA FIND?

The Dupont Warning Letter issued in December 2022 states that the agency considers the microcrystalline cellulose excipient in

question, Avicel®, adulterated because its controls for manufacturing, processing, packing, or holding do not conform to GMP, and because the excipient failed to conform to compendial standards for strength, quality, or purity.

The letter supports this overall contention by listing five main deficiencies, each with supporting examples:

1. "Your firm failed to perform adequate investigation of complaints.
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.
3. Your firm failed to ensure the test methods used are suitable for their intended use.
4. Your firm failed to have an adequate change management program to evaluate and approve changes that may impact the quality of the excipient.
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."

In addition, the agency includes a section on "Data Integrity Remediation" that begins with the statement, "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." More below on data integrity.

HOW DOES THIS LETTER DIFFER FROM DRUG GMP WARNING LETTERS?

The Dupont letter, like warning letters to drug manufacturers, details alleged violations of federal law. It is similar in that many of the deficiencies are the same as found in drug companies, such as issues with investigations and identification of root cause, change management, and implementation of corrective actions and preventive actions (CAPAs).

Unlike warning letters to FDF drug manufacturers, FDA cites only the FD&C Act, which is very general and high-level, rather than specific violations of the CFR, because excipients are not covered under the CFR.

Evaluating FDA compliance actions like warning letters and Form 483s is a good way to determine agency expectations and to focus internal evaluations of manufacturing facilities and quality systems.

FDA warning letters to finished dose manufacturers include numbered paragraphs with a reference to the specific CFR that is being cited followed by examples that support the citations. For example:

> **Your firm failed to thoroughly investigate any unexplained discrepancy or failure of a batch or any of its components to meet any of its specifications, whether or not the batch has already been distributed (21 CFR 211.192).**
>
> For example, your investigations into out-of-specification (OOS) results and process deviations were inadequate…(68 more words in the example text)

In the letter to Dupont, there are numbered paragraphs, but no CFR codes to guide us in determining which quality systems need our attention.

THE QUALITY SYSTEMS

The FDA "quality system model" is an organization scheme used by the agency since 2006 to categorize aspects of drug

manufacturing into meaningful systems that can be used by agency investigators during manufacturing facility inspections and by drug companies to organize compliance efforts. While the agency uses six quality systems, at Redica Systems, we add a seventh system – data integrity.

It is helpful for drug companies to map issues found on inspection to the quality systems and to subcategories of those systems to target improvement efforts.

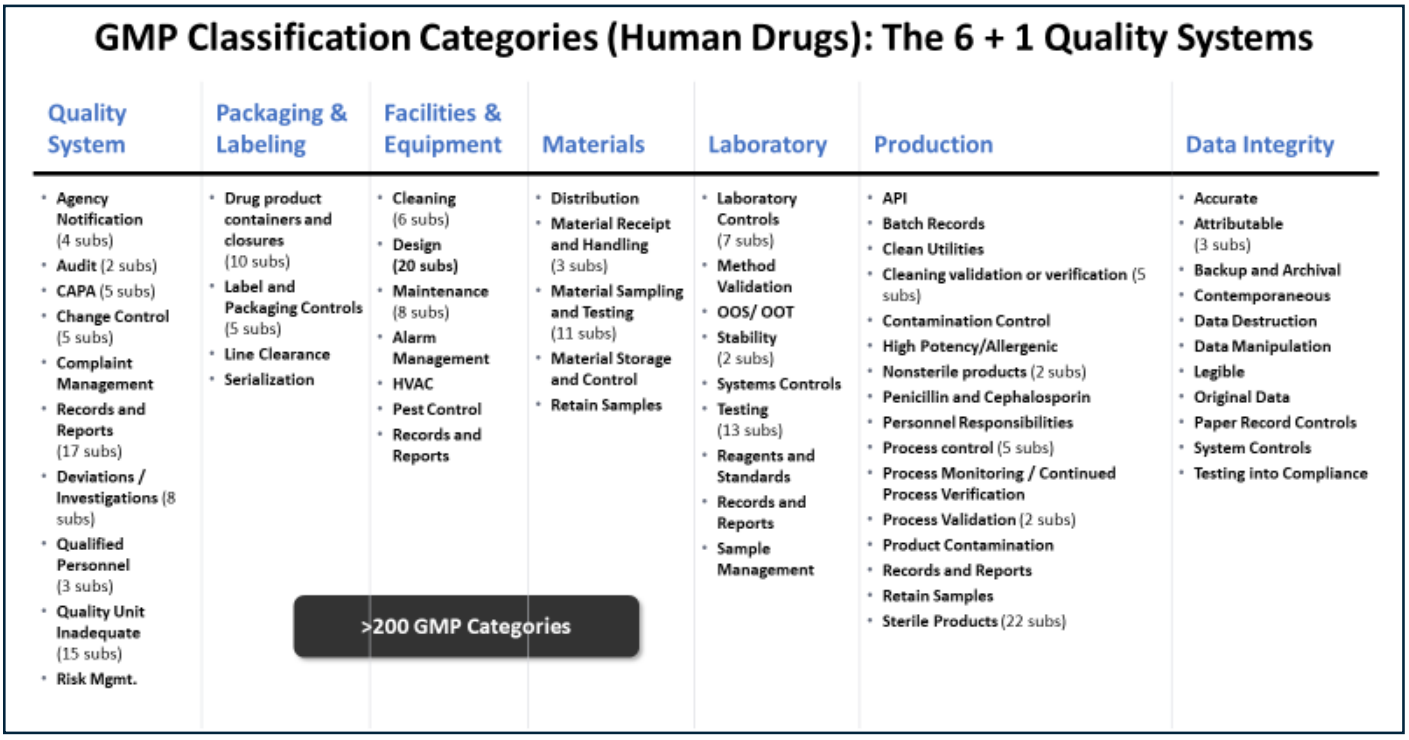

FIGURE 3 | THE 6 + 1 QUALITY SYSTEMS

At Redica Systems, we have used Artificial Intelligence and Natural Language Processing tools to isolate language used in these documents and create a computer algorithm, the Quality System Labeling (QSL) model, that evaluates observations and citations and maps them back to the Quality Systems and subsequently to an inferred CFR. This is especially useful in documents that do not cite the CFR. It is also useful in drug GMP warning letters to evaluate language used in the example supporting text that point to additional deficiencies that we call "hiding in plain sight."

An analysis of the second citation in the Dupont letter and the two paragraphs following by our QSL model shows how the language in the letter (left column) maps to specific quality system areas and the corresponding CFRs (right column) for both the primary citation (in **bold**) and the supporting example text found in **Figure 4.**

An evaluation of the complete letter gives deep insights into the issues FDA found and which quality systems they map to, which is valuable for helping guide remediation efforts.

SUMMARY OF MODEL FINDINGS FOR DUPONT WARNING LETTER

Deficiencies found in the Dupont letter by the QSL model were mapped to the Production, Materials, Laboratory, Quality, and Data Integrity systems and are summarized here in order of prevalence also found in **Figure 5**.

– 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.

Example Tagging from the Redica Systems QSL Model

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 **(211.192)**
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 **(211.192)**
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 **(211.180(d))** Laboratory|OOS / OOT **(211.192)**
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.	Laboratory|Laboratory Controls|Impurity Control **(211.160(b))**

FIGURE 4 | EXAMPLE TAGGING FROM THE REDICA SYSTEMS QSL MODEL

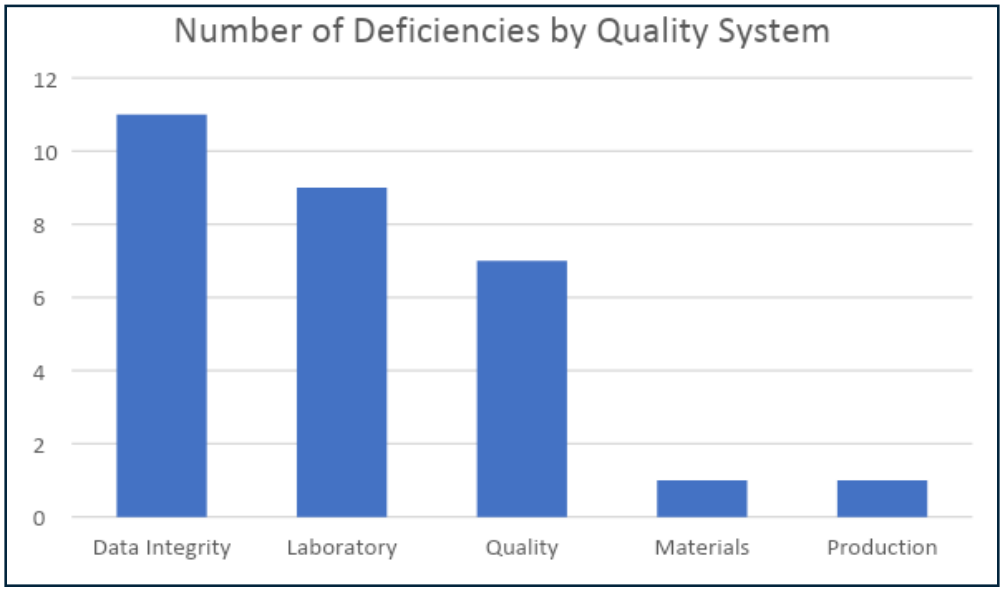

FIGURE 5 | NUMBER OF DEFICIENCIES BY QUALITY SYSTEM

WHAT IS THE RISK?

A focus on pharmaceutical excipients appears new for FDA. However, it is actually an extension of the agency's expectations for oversight of suppliers by drug manufacturing companies and compliance with the FDA Quality Agreement Guidance.

For example, in June 2017, a Contract Manufacturing Organization (CMO), ChemRite CoPac in Wisconsin, was making oral pharmaceutical solutions for another company using the same equipment it used to make toxic car washes and waxes without appropriate cleaning in between. It was cited in a warning letter for, among other things, the lack of a quality agreement with the firm that it was making the solutions for (Sage Products).

The FDA sent a similar warning letter to Sage Products in July 2017 for the lax oversight of the contractor (ChemRite CoPac) that was producing the oral solutions. This is what one FDA investigator calls a "twofer"—two warning letters from one inspection. One was to the product owner and one to the CMO.

In the case of a prominent excipient, Avicel, quality issues with the excipient as identified at the manufacturing site have been made public in a warning letter, putting all drug companies who use the excipient on notice that they are using a product in the formulation of their drug that is potentially adulterated. Notably, the warning letter says the Avicel excipient is "extensively used as a major component in a wide variety of drug products." It is possible by extrapolation that users of the excipient may be at risk for regulatory action as well.

WHAT SHOULD COMPANIES DO?

FDF manufacturers: Ensure that your on-site audits of excipient suppliers are robust and well-documented, with any issues addressed. Also ensure you have a robust excipient qualification program and your suppliers are qualified. Keep informed on FDA warning letters and import alerts and compare those against your list of suppliers, taking action if necessary.

Excipient manufacturers: Study the Dupont warning letter and the quality system areas where the deficiencies were found to evaluate your operations against the issues FDA found there. Ensure your quality systems are robust.

ABOUT THE AUTHOR

Jerry Chapman is Senior GMP Quality Expert at Redica Systems. He brings over 40 years' experience in the pharma industry, including 31 years at Eli Lilly, where he worked in product development, biosynthetic human insulin manufacturing, and site and corporate quality. He designed and implemented a comprehensive GMP Intelligence process to identify, analyze, and archive pertinent drug GMP regulations, inspection findings, trends, and best practices in the U.S. and internationally.

Chapman has been an invited speaker at PDA, AAPS, ISPE, and RAPS events and has served as a consultant to the animal health and compounding pharmacy industries. He founded the Midwest Discussion Group GMP-Intelligence sub-group and chaired it from 2004-2009. At Redica Systems, Chapman works with the machine learning and data science teams building computer models that examine enforcement actions and other data to produce insightful expert analyses. His articles appear on the Redica Systems Conference Spotlight page.