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REPORT

Insights on Quality from FDA Leaders

The following bundle contains six articles covering sessions featuring FDA regulators at the 2022 PDA/FDA Joint Regulatory Conference.

- FDA on Compliance Issues in Pharma
- Where is My EIR?
- Who Decides if My FDA Inspection is Classified OAI?
- Why am I Being Inspected Again So Soon After a Pre-Approval Inspection?
- Senior Management Failures Lead to Patient Deaths, Prison Sentence
- Persistent Non-Compliance Leads to a Consent Decree

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PART I: FDA ON COMPLIANCE ISSUES IN PHARMA

During a Q&A session at the [2022 PDA/FDA Joint Regulatory Conference](#) in mid-September in Washington, D.C., CDER Office of Compliance Director [Donald Ashley](#) and Office Director of the Office of Manufacturing Quality [Francis Godwin](#) provided insight regarding compliance issues in pharma companies.

The following questions from attendees were among those addressed:

- What factors are considered by FDA when determining inspection classification and the agency response?
- Why do some companies seem to have persistent compliance issues?
- What is recommended when responding to 483 observations?

Question: When your office is reviewing an Official Action Indicated (OAI) case, do you take the firm’s compliance history into account?

“Yes, we do,” Godwin stated. “One of the questions when we are looking at an inspection outcome, or sample outcome is, ‘Is this the same as it was before, or is it something different?’ That is based in part on what other information we have. If it is the first time we have ever been there, we do not really know much about it. So, we are assuming it is a clear picture.

“But we do know that there are trajectories. Sometimes firms

are in an episodic event where they are in and out of compliance. Sometimes they are much higher and we are looking at the calculus to say, ‘Is this a firm that has been in and out of compliance, has gotten warning letters, and been cleaned up?’

“We would also ask ourselves, ‘Are they falling down again, and do we need to get them back up? Or is this a firm that is much more mature, has a higher level of quality and they slipped, so we just need to help them a little bit? And that is where we may schedule a regulatory meeting versus something more aggressive.”

Question: Why do you think some companies have persistent compliance issues while others have strong compliance records?

“It gets back to some of the myths and misconceptions that I talked about during my presentation,” Ashley replied. “There are people who think they should just do the absolute minimum to meet the lowest possible level of quality that they think will get them to pass an inspection.

“Presumably they think it is because doing more is going to be too costly. But the truth of the matter is that negative consequences flow from those types of actions and in the long run end up costing the companies more.

“Then by contrast there are people who understand actual quality management systems (QMS). It is going to be good for patients, it is going to be good for the quality of the product. But in the long run, it also can be good for the company too because it

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offers predictability and a positive reputation for the company.”

Question: Do you have any recommendations on how 483 responses can be improved so they lead to more sustainable solutions and corrections?

“If you have an FDA inspection and you get issued a 483,” Godwin began, “understand that when FDA looks at the response, we are going to ask, ‘are the findings the tip of the iceberg, or is this it? Is this something unique?’

“One of the things we recommend is that when you are creating a 483 response, do not just look at the one thing that was cited in the 483. Investigators are there for a few days. They are not going to do a complete audit of everything. They are going to look for examples and point them out. And so, we are asking, ‘is this the tip of the iceberg?’

“Also, is it the same everywhere? Say, as an example, that an investigator finds that you missed a stability sampling and testing time point and your response is, ‘yes, we did. We went back and tested that one sample. It is good.’ When we review that, we are going to have the question, ‘What about the rest of them? Did you test any of the others? What is going on?’

“21 CFR 211.192 is kind of the bread and butter CFR for quality oversight of systems. If you find a problem you look at it. Also, look at it and ask, is this problem limited to here or does it affect other things?

“And when you are crafting a 483 response, keep that in mind because you want to look at what was found by the investigators and understand what is going on. FDA is going to ask, ‘Is this a bigger thing that affects other drugs or other lots?’ That really helps us in terms of knowing what to do.”

PART II: WHERE IS MY EIR?

Have you wondered why, after an FDA inspection that is classified No Action Indicated (NAI) or Voluntary Action Indicated (VAI), the inspected firm is given a copy of the Establishment Inspection Report (EIR) relatively quickly, but when an Official Action Indicated (OAI) classification is assigned, the EIR is not sent?

During a Q&A session at the conference, CDER Director of the Office of Manufacturing Quality Francis Godwin explained why drug firms generally do not receive a copy of the EIR immediate-

ly when they receive an OAI classification.

“It is a complicated question in that it is governed in part by disclosure law,” Godwin said. “An EIR is a federal document and is subject to the Freedom of Information Act (FOIA). In FOIA, there are certain exemptions.

“When we send an NAI (No Action Indicated) or VAI (Voluntary Action Indicated) classification letter we will provide a courtesy copy of the EIR. Historically, redaction lawyers received so many FOIA requests from every firm that was inspected that they recommended it was better to incorporate sending the EIRs as a matter of business when the inspection is ‘closed.’” That is what happens now.

“I put ‘closed’ into quotes because that is what the regulations say. The regulation is [21 CFR 20.64](#), which covers disclosure of FDA-related documents. If you look at a warning letter posted on our website you will see it is redacted, for example, with the code (b)(4).”

Exemption (b)(4) of FOIA permits agencies, as a matter of discretion, to withhold trade secrets and commercial or financial information obtained from a person which is privileged or confidential.

“There are other exemptions—for example, if there is a confidential informant, that will not be disclosed.

“There is also an exemption if the regulatory action is still pending and the matter is not considered closed. For most of FDA, when a firm is OAI, the regulatory action has already been taken, whether it is a warning letter, a regulatory meeting, or something else. In those cases, the matter is closed and it can be shared.

“However, as a result of the [Generic Drug User Fee Amendments II \(GDUFA II\)](#) and FDA’s ‘Concept of Operations’ (Con-Ops) we are letting firms know the OAI status before the regulatory action is taken. So, you will be told you are OAI but the EIR is not shareable because of the way the disclosure regulations are set up.”

ADDITIONAL RESOURCE

[FMD-145 – Release of the Establishment Inspection Report \(EIR\)](#)

PART III: WHO DECIDES IF MY FDA INSPECTION IS CLASSIFIED OAI?

Who decides how inspection results are interpreted and who decides how an inspection becomes classified as Official Action Indicated (OAI) rather than Voluntary Action Indicated (VAI) or No Action Indicated (NAI)? And how much influence does the investigator who performed the inspection have on that decision?

This topic was addressed during the “Lunch with the Regulators” session. The process the agency uses, the players, and the role of the Consumer Safety Officer (CSO)—the agency investigator—was elucidated by CDER and Office of Regulatory Affairs (ORA) personnel in response to a question at the lunch session regarding how an OAI classification is determined.

THE PROCESS BEGINS WITH THE INVESTIGATOR

ORA Division of Pharmaceutical Quality Operations Director [Jeffrey Meng](#) began the discussion by explaining that the process starts with the CSOs. Investigators are trained to perform inspections and to find issues and they need to determine if those issues are significant and systemic.

FDA compliance programs and policy documents help guide investigators on how to view their findings and how to document, from an evidentiary standpoint, whether they are significant. However, the observations are just that—observations made during the inspection from the investigator’s viewpoint.

The next piece of information that comes into play is the response by the firm to the observations, potentially including documentation of any corrective actions that have been taken or are planned.

FDA staff writes a report, marrying together the investigator’s findings and the firm’s response, and that report is reviewed by agency supervisors and sent to ORA for cases where the investigator is recommending a compliance review.

A key point from Meng’s discussion is that FDA investigators make initial recommendations, after which further review takes place. If the firm’s responses are not deemed adequate or the risk not appropriately mitigated, compliance officers in ORA will generate a recommendation package for potential action that will be sent to CDER or, potentially, to the Center for Veterinary

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Medicine (CVM) compliance office.

THE ROLE OF THE COMPLIANCE OFFICER

CDER Office of Compliance Senior Policy Advisor [Brooke Higgins](#) continued the explanation from her point of view. Compliance officers perform an initial evaluation of the Establishment Inspection Report (EIR)—the investigator’s documentation of the inspection—the exhibits that come with it, the recommendation memo that comes from the ORA compliance officer, and an analysis of the 483 response the firm submitted, she said.

The team leads and branch chief and division director, along with policy personnel, do an initial evaluation and come up with a recommendation that is proposed in a meeting with the office director. If there are any questions, the team can reach out to the ORA compliance officer to get information from the investigator.

Part of the evaluation, Higgins explained, includes performing a drug shortage evaluation if that is a potential issue. There are additional consultations—for example, regarding chemistry or microbiology— and involvement of any other potentially impacted center, such as CVM for an animal health product or CDRH for a combination product. That additional information is provided to the office director to help inform the final classification decision.

A COMPLICATED PROCESS, WITH GOOD REASON

CDER Office of Manufacturing and Product Quality Division Director [Carmelo Rosa](#) also weighed in on the process. He noted that the OAI decision involves a group effort and has been vetted through a “very complicated process—but complicated in a good way.” He also stressed the importance of 483 responses

and pointed out that deficiencies in the responses can prompt warning letters to be issued.

The OAI decision, Rosa said, is based on many elements, including evidence from the inspection, the content of the 483 response, the history of the firm, the risk to patients from the deficiencies found, and whether the observations include repeats from previous inspections of the facility or another facility in the same company.

After the OAI classification is determined, another session is held to decide whether the resulting action will be a regulatory meeting or a warning letter.

Returning to the original question of how much influence the investigator performing the inspection has on the process, Rosa reiterated that the investigator does not decide whether a warning letter is issued. The investigator collects the facts, the evidence, discussions, and interactions that take place, and what occurred during the inspection, all of which is considered along with all the other elements mentioned above.

AT THE INTERSECTION OF SCIENCE AND LAW

ORA's Meng further emphasized the collaborative nature of the process, and the reason so many players and experts are involved.

FDA is “at the intersection of science and law,” he commented. “It is a law enforcement agency that makes decisions based on science.”

Because the Code of Federal Regulations (CFR) is a set of administrative laws, violations of the CFR are violations of the law. In other words, there is a legal standard that is not being met, such as GMP adulteration or misbranding. If the agency is going to impose regulatory or judicial action, it must meet the standard that the law requires.

To that end, FDA has attorneys—regulatory counsels—who are included in the reviews and composition of warning letters, because the actions must meet legal standards.

The language is important: Agency investigators make “observations” on 483s, whereas a warning letter contains “citations,” i.e., citing violations of the law.

It is important to remember that CFR citations in a warning letter are violations of federal law and should always be taken seriously, as should any responses to the agency.



[Related: Looking for recent 483 observations from human drug GMP inspections? Contact us for a [FREE 483 Observation Report](#) for a taste of our actionable intelligence.]

PART IV: WHY AM I BEING INSPECTED AGAIN SO SOON AFTER A PRE-APPROVAL INSPECTION?

Does successful completion of an FDA pre-approval inspection (PAI) influence the timing of a subsequent surveillance inspection? And should it?

This topic was addressed during the “Lunch with the Regulators” session.

ORA) Division of Pharmaceutical Quality Operations Director Jeffrey Meng explained that PAIs and surveillance inspections are very different types of inspections, but because they are both agency inspections they may be perceived similarly.

In a PAI, he said, the objective is to cover readiness for commercial manufacturing. It focuses on the systems that govern the product that is the subject of the inspection.

Surveillance inspections, however, are different, as they cover the entire site. And since they are not equivalent, FDA would not waive a surveillance inspection because of a recent successful PAI. So, in general, having a PAI will not change the scheduling of a surveillance inspection.

CDER Office of Pharmaceutical Manufacturing Assessment Deputy Director [Derek Smith](#) noted that after a PAI is passed, the site enters the site selection model. This model is risk-based and considers numerous factors that impact when the next sur-

veillance inspection will occur, taking into account a variety of quality signals such as Field Alert Reports (FARs) and Biological Product Deviation Reports (BPDRs).

Meng further explained that FDA tries to be efficient with inspection resources. He remarked that if a site comes up for a surveillance inspection at the same time as a PAI for the same site, the agency will work to combine those operations and assign investigators to conduct both at the same time, if possible.

Center for Veterinary Medicine (CVM) Pre-Approval Facilities Assessment Program Lead Laura Huffman also commented on the two inspection types. A PAI, she pointed out, is targeted, and uses information from the application. Whereas a surveillance inspection is more general, a PAI is “focused like a laser beam.” She noted that since the question comes up frequently perhaps the agency needs to do a better job communicating the purpose of each of those inspection types.

PART V: SENIOR MANAGEMENT FAILURES LEAD TO PATIENT DEATHS, PRISON SENTENCE

What happens when a U.S. pharma company markets a product that is seriously contaminated and causes illness and death? Among other things, FDA investigates. What happens when the company’s senior management fails to make changes promised to the agency to prevent those outcomes from recurring and more illnesses and deaths result? And what happens to senior company management who misrepresent the company’s actions to the agency?

At the [2022 PDA/FDA Joint Regulatory Conference](#), FDA CDER Office of Compliance Director [Donald Ashley](#) told a tale of those events happening, and the legal action his agency took against the company involved.

The case involves, “frankly, one of the most egregious violations that I have seen during my nearly six years as director of CDER Compliance,” Ashley stressed.

The story begins in 2016. The CDC and FDA were investigating a multistate *Burkholderia cepacia* outbreak that included more than 60 confirmed cases across 12 states. Several deaths were associated with the outbreak. *B. cepacia* is a gram-negative bacterium that is usually not harmful to healthy adults but can lead to respiratory and other infections in people with weak immune systems, chronic lung disease, and other conditions.

Testing by FDA and CDC confirmed that the infections were linked to contaminated product made by Florida-based PharmaTech, LLC. An FDA inspection of the company’s manufacturing facility identified *B. cepacia* in more than ten lots of the firm’s oral liquid docusate sodium product, known as Diocto Liquid. The inspection also detected *B. cepacia* in the water system used to manufacture the product..

In response to the inspection findings, PharmaTech CEO Raidel Figueroa advised FDA that PharmaTech had ceased production and was going to re-engineer the purified water system to prevent future contamination.

“And this is where the situation really went from bad to much, much worse,” Ashley lamented. In March 2017, FDA learned that PharmaTech had re-started production.

The agency conducted a reinspection that month. During the inspection, “Figueroa repeatedly lied to the FDA,” Ashley asserted. “For example, he lied by excluding his docusate sodium product from the list that was provided to the FDA when we asked him to disclose all the products that the firm had resumed manufacturing. The firm had actually shipped 7,000 units of that product earlier that month.

“They also lied by falsely saying to FDA that PharmaTech’s new water system had met acceptance criteria, which was not true,” the CDER compliance director stated.

About three or four months later, in July 2017, the CDC notified FDA of a second round of multiple *B. cepacia* infections in pediatric patients at Stanford Children’s Health and Lucile Packard Children’s Hospital in Palo Alto, Calif., and Johns Hopkins Children’s Center in Baltimore, Md.

FDA investigated, collecting bottles of Diocto Liquid from those medical centers. Several of the bottles contained unacceptable amounts of bacteria, yeast, and mold, according to FDA lab testing. Some bottles tested positive for *B. cepacia*. The FDA and CDC traced the product back to PharmaTech—product that was distributed in March of 2017. More deaths were associated with the second outbreak.

“In this instance, PharmaTech even refused to recall the product,” Ashley reported. “We had to work directly with the downstream distributors of the product to effect a recall to get it all off of the market.”

The agency immediately referred the case to its Office of Crimi-

nal Investigations.

In June 2022, Figueroa pled guilty to conspiring to defraud the FDA, falsifying records in an FDA investigation, obstructing proceedings before the FDA, and distributing adulterated drugs. In August 2022, he was [sentenced to 37 months in prison](#). Parents of victims that died during the *B. cepacia* outbreaks testified at the sentencing hearing.

Ashley characterized the case as “egregious, obviously for a number of factors, including total disregard for patient safety by senior company management, total disregard for quality, false statements made to the FDA during the inspection, of course, and the absolutely tragic consequences that resulted.”

PART VI: PERSISTENT NON-COMPLIANCE LEADS TO A CONSENT DECREE

Persistent: (adj): existing for a long or longer than usual time or continuously

Non-compliance (noun): failure or refusal to comply with something (such as a rule or regulation): a state of not being in compliance

(Both definitions taken from Merriam-Webster.com.)

Put these two words together in the pharma world and the combination creates a recipe for potential harm to patients and serious legal action, with the pharma company exhibiting this behavior likely to receive an FDA warning letter and possibly become the defendant in a suit filed by the U.S. Department of Justice (DOJ).

Specifically, what happens when a pharma company fails to have adequate procedures to prevent cross-contamination of equipment, fails to reject drug lots using a contaminated ingredient, and fails to fully investigate the root cause of such contamination? And what happens when these failures are discovered repeatedly during inspections, even after the company has been warned to correct them?

FDA CDER Office of Compliance Director Donald Ashley presented a case study that traced the inspection and compliance history of Morton Grove, where those issues occurred. Morton Grove is an Illinois-based drug manufacturer that makes both over-the-counter and generic drugs and is owned by Mumbai, India-based Wockhardt.

“We had inspected the firm several times over the years,” Ashley noted, “but things took a turn for the worse,” when an early 2016 inspection found violations related to:

- Inadequate investigations for out-of-specification results
- Repeating tests until a passing result was found
- Inadequate process validation “which was probably an underlying root cause source of a lot of the other problems that they were experiencing”
- Widespread multiple concerns with data integrity

FDA issued a [warning letter](#) to the firm citing these violations in February 2017.

The letter also cites concerns the agency had with senior management’s oversight and approach to quality issues—not just at the Morton Grove facility, but also at other facilities owned by Wockhardt.

Not surprising given the well-known mantra that “quality culture is pervasive.”

On inspection, FDA personnel observed that the firm was conducting investigations of quality-related problems, “but they were doing it outside of the quality unit, specifically, so investigations would not be covered by the quality unit procedures,” Ashley asserted.

He said the owner of the company had a pattern of running poor quality manufacturing sites—sites that had received FDA warning letters and import alerts for similar CGMP violations, including for data integrity, and in particular for poor investigations into failing results.

“To say the least, the firm had an extremely poor quality culture resulting in no small part from poor leadership by senior management,” the CDER compliance director said.

Here is an excerpt from the warning letter:

“At this time, seven Wockhardt facilities (including Morton Grove) are considered out of compliance with CGMP. These repeated failures at multiple sites demonstrate your company’s inadequate oversight and control over the manufacture of drugs.

“In your responses to the various actions listed above, including during multiple meetings with FDA, you have repeatedly discussed and promised corporate-wide corrective actions. Yet, when FDA inspects or returns to other Wockhardt facilities, sim-

ilar violations are shown to persist.

“Your executive management remains responsible for fully resolving all deficiencies and ensuring ongoing CGMP compliance. You should immediately and comprehensively assess your company’s global manufacturing operations to ensure that systems and processes, and ultimately, the products manufactured, conform to FDA requirements.”

The letter listed repeat violations and deviations at multiple sites owned by Wockhardt, including an overview of which sites had previously received a warning letter or been placed on U.S. Import Alert (**Figure 1**).

Subsequent to the 2017 warning letter, FDA reinspected the Morton Grove facility twice, once in 2019 and then again in 2021, and the data integrity issues “just got worse” Ashley stressed. “So, even after we had alerted the site to our concerns over data integrity in the 2017 warning letter, upon reinspection, we found that backdating of microbial test results was actually condoned by the facility management. That, for us, really called into question the validity of any of the test results at the site.”

Also discovered was evidence of serious cleaning deficiencies

as well as microbial contamination of drugs.

Ashley provided photographic examples of the observations that agency investigators reported upon reinspection (**Figure 2**). The photo on the left shows the inside of a piece of equipment that had been marked clean, however, “you can easily see the drug residue on those product contact surfaces, so the material could have readily transferred and contaminated the next batch made with that equipment,” he pointed out.

“And on the right, you can see rust and chipped paint on a motor that was directly above an opening in a tank, and so that allowed the rust to fall directly into the tank and contaminate the drugs.” Given the lab testing integrity issues seen previously, the agency was concerned that testing would not find these contamination events had they occurred.

Due to the widespread and escalating quality concerns that were identified at the facility, FDA worked with DOJ to seek relief through the courts.

In August 2022, an Illinois federal judge approved a consent decree of permanent injunction. It states, in part, “the negotiated consent decree entered by the court permanently enjoins the

Excerpt from FDA Warning Letter to Morton Grove February 2017

Repeat violations and deviations at multiple sites since 2013 at other Wockhardt facilities (*emphasis added*).

Wockhardt Waluj, FEI 3005289335, was placed on Import Alert on May 22, 2013, and was issued a Warning Letter dated July 18, 2013, for, among other things, **limiting an FDA inspection and manipulating and deleting data**.

Wockhardt Chikalthana, FEI 3002808503, was issued a Warning Letter on November 25, 2013, and was placed on Import Alert on November 26, 2013, for, among other things, **manipulating and deleting data**.

Wockhardt Waluj, FEI 3004540156, was issued a Warning Letter on November 25, 2013 for, among other things, **manipulating and deleting data and deficient in-process testing practices**.

CP Pharma, FEI 3003369660, was issued a Warning Letter on November 16, 2016, for **poor aseptic practices and environmental monitoring** in the manufacture of sterile drugs.

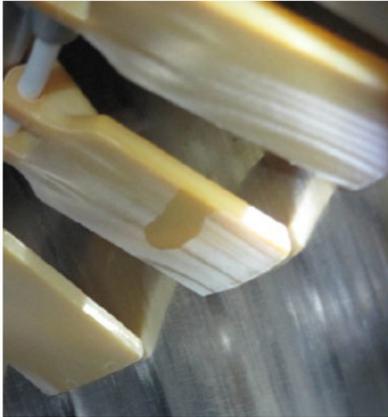
Wockhardt Ankleshwar, FEI 3002808500, was placed on Import Alert on August 5, 2016, and received a Warning Letter on December 23, 2016, for **data manipulation and destruction, and poor aseptic practices** in the manufacture of sterile drugs.

Wockhardt Shendra, FEI 3009278506, received an Untitled Letter on January 27, 2017, for **manipulating and deleting data and poor aseptic practices** in the manufacture of sterile drugs.

FIGURE 1 | Excerpt from FDA Warning Letter to Morton Grove February 2017

Examples of What FDA Found on Re-Inspection

Drug residue in equipment marked as “clean”, which can contaminate the next batch



Poorly maintained equipment, with potential for rust flakes to fall in production equipment



FIGURE 2 | What FDA Found on Re-Inspection

defendants from violating the FDCA, and requires, among other things, that the defendants stop manufacturing, processing, labeling, holding, or distributing adulterated drugs. Further, the defendants must destroy all drugs in the facility, except for those that are medically necessary.”

As for the other sites that were mentioned in the warning letter to Morton Grove, all but one of those remain on import alert or are no longer in the U.S. supply chain, Ashley reported.