Denise Myshko

Preparing for a Successful FDA Inspection

Pharmaceutical manufacturers need to be inspection ready, aligning their organization with the expectations of regulators.

Preparing for successful inspections is not a one-time event. Being inspection ready means that pharmaceutical leaders are committed to managing compliance as part of their company culture. Industry experts say successfully managing compliance is something that is done every day and not something done to prepare for an inspection by Food and Drug Administration regulators.

Being inspection ready is a state of maturity, says Lauren Stewart, VP, quality and compliance, at Telerx.

"Inspection readiness is having a quality management system that doesn't need any lead time for an inspection," she says. "People adhere to SOPs, internal audits are conducted regularly, and there is detailed CAPA management. But this costs money and requires investing in the disciplines needed to remain in an inspection-ready state."

Being inspection ready at all times is good for business. Overall, companies that embrace regulations are generally more financially successful than their peers, says Craig Wylie, partner at PA Consulting. In fact, PA Consulting research shows that there is a 29% correlation between a company's shareholder value and how effectively that company prioritizes and manages being regulatory compliant.

"Companies that do better in the market and have better shareholder return are better at managing their regulatory and compliance issues," Mr. Wylie says. "I wouldn't say it's causal, but there is definitely a correlation."

People often view the inspection process the wrong way, says Richard Moroney, Ph.D., life sciences and regulatory expert, at PA Consulting.

"Some people think they must be doing okay because the inspector gives the company a clean bill of health," he says. "But that is a recipe for failure because the company has to be confident that it is doing the right things before getting any feedback from the inspector."

Dr. Moroney says people within the industry often view the inspection process as an excessive burden and set up an antagonistic relationship with regulators.

"Ultimately, the inspection process is about companies demonstrating that they are doing what they've said they will do," he says. "When viewed from that perspective, companies can have a more engaged conversation that builds trust faster with inspectors."

Mr. Wylie says the mistake people make is to treat inspections like events as opposed to a way of life.

"Managers have to be thinking about compliance all the time," he says. "I've had people say to me 'We're lucky the inspectors didn't ask about X' My response is that if you know there is a problem, you should fix it, which is what inspectors expect you to do."

Ms. Stewart says companies that aren't making compliance a way of life are not placing resources where they are needed to maintain SOPs.

"The mistake that companies make is that they aren't driving quality by culture, lived by all, and driven from the top down," she says. "Often when companies make mistakes, they are not valuing the importance and criticality of investing in themselves."

What the FDA Looks For

According to officials at the FDA, many factors are considered when talking about scheduling an inspection of an FDA-regulated company. In general, the agency tries to inspect drug manufacturers every two years. The Food and Drug Administration Safety and Innovation Act requires the FDA to replace the previous two-year drug inspectional frequency requirement with a risk-based inspection schedule for domestic and foreign drug facilities. Inspection criteria include the company's compliance history and the inherent risk of the drug being manufactured. The FDA is developing risk-based methodologies for inspections and is working to establish common risk principles across the various centers.

The FDA conducts several types of inspections: preapproval inspections after a company submits a marketing application; routine inspections of a regulated facility; and for-cause inspections to investigate a specific problem that has come to the FDA's attention.

The FDA will also inspect manufacturing facilities after a merger or acquisition, Ms. Stewart says.

"The FDA gives companies about 18 months following a merger or acquisition for integration of people, process, and systems," she says. "After that, the expectation is that the company will be operating as one."

Most Frequent Issues Cited at Inspections

- Procedures not in writing or not fully followed
- Investigations of discrepancies, failures
- Unscientifically sound laboratory controls
- Absence of written procedures
- SOPs not followed/documented
- Absence of control procedures to monitor and validate performance
- Written procedures not established or followed
- Documented training: operations, GMPs, written procedures
- Cleaning/sanitizing/maintenance issues
- Testing and release for distribution

Source: PA Consulting

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>
> **CRAIG WYLIE** / PA Consulting

> "Ultimately, the inspection process is about companies demonstrating that they are doing what they've said they will do."
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> **DR. RICHARD MORONEY** / PA Consulting

> "The focus of every inspection is quality, which is the ability to demonstrate that a company is in control of its people, processes, and systems."
>
> **LAUREN STEWART** / Telerx

Ms. Stewart says for-cause inspections can be triggered by late reporting of adverse events.

The FDA also inspects pharmaceutical manufacturing facilities to make sure they meet current good manufacturing practice (cGMPs). The FDA relies upon reports of potentially defective drug products from the public and the industry. The FDA will often use these reports to identify sites for which an inspection or investigation is needed. Most companies that are inspected are found to be fully compliant with the cGMP regulations, according to regulators.

An inspection, Ms. Stewart says, is about people, process, and systems.

"Regulators will look at whether people are trained and qualified to perform the role," she says. "They will look at SOPs and the procedures that govern the reporting of side effects and pharmacovigilance. They will look for evidence that every case is processed per the documented procedures. There is high scrutiny on whether the procedural controls are being adhered to. And the FDA will look at the systems and technology: is the drug safety database secure; is access controlled; is it a validated system; is it CFR part 11 compliant? These are guiding principles that the FDA expects of any company operating in this space."

The focus of every inspection is quality, Ms. Stewart says.

"Regulators are looking for compliance with SOPs," she says. "They have to be part of everyone's behavior and the company is able to demonstrate control of its employees' training and qualifying the resources of the people performing this pharmacovigilance service. Data must be secure; healthcare information must be private and must follow the governing principles of HIPAA and data privacy."

Mr. Wylie says inspectors think systematically.

"If there is a problem, inspectors assume the problem will be fixed immediately," he says. "What they are really worried about are the problems they haven't found."

Mr. Wylie provides an example of a company that was doing validation testing of its systems. Errors were being recorded as a failed test instead of indicating the reason for the error. This was done because the test operator didn't speak English as his first language, and recording a failed test was easier for the operator than entering the actual reason for the failure.

"The inspector then questioned how everyone was to know that a successful test was, in fact, successful since the operator didn't understand what he was entering," Mr. Wylie says. "The company saw this as needing to fix a few codes, but the inspector was worried the company didn't properly train its people on why they were recording this information or on how to use the system."

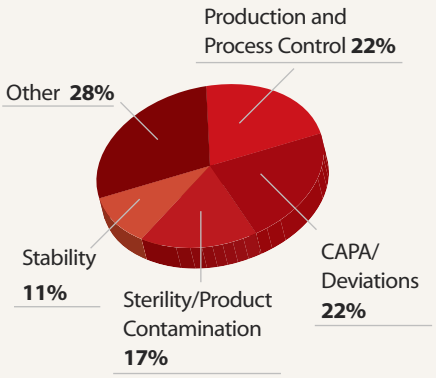
Each year about 70% of GMP violations are in product and process controls (P&PC), CAPAs/deviations, sterility, and stability, according to an analysis by PA Consulting of warning letters issued by the FDA's Center for Drug Evaluation and Research.

"These are simple things to correct and avoid," Mr. Wylie says. "Inspectors don't come in with CSI-level forensic analytics. They ask to see the process. The reality is that organizations are trying to do the best they can. I suspect that people within these organizations are asking the right questions about their processes, but they aren't asking the right people or at the right time."

Best Practices

Industry experts say best practices in inspection readiness include designing processes and systems to achieve quality and safety.

Areas of GMP Violations



Source: PA Consulting

Dr. Moroney stresses that companies have to take quality seriously.

"Leadership has to be on board with having and maintaining the highest quality systems," he says. "Leaders have to make sure that there are checks and balances within the organization and within the quality assurance group that can reasonably influence the production group so that what needs to be done can be done. When things break down, the message about doing the right thing must come from the top. If a company strives to always do what's right, they will be ready for the inspection."

Mr. Wylie says inspectors look to companies to demonstrate they are in control of their quality systems.

"They want to see that organizations are finding problems, addressing those problems, addressing systemic errors, and putting in place metrics and management processes," he says. "Thinking like an inspector involves change management. And that inspection readiness is entirely driven around people." PV