THE COMPLETE GUIDE TO COMPLIANCE REMEDIATION PROJECTS

How to remedy the root causes of compliance issues: A whitepaper

THE FDA GROUP LLC

TABLE OF CONTENTS

INTRODUCTION

Jackelyn Rodriguez, a regulatory expert with over 30 years of experience in compliance consulting sums up the state of pharmaceuticals in simple terms:

"Regulatory compliance has never been more important or more difficult."

Over the past 15 years, the U.S. FDA has tightened regulations on pharmaceutical, biotechnology and medical device companies—a difficult shift in a time where restructuring and corporate consolidation have only made these challenges more difficult to overcome.

When ignored, Rodriguez says these problems can lead to *"crucial lapses in oversight and quality management, opening the door to a host of compliance risks and enforcement actions, such as an FDA 483 list of inspectional observations, warning letters, consent Decrees, and fines, which can cost millions of dollars."*

To prevent potentially damaging consequences when things do go wrong, it's up to manufacturers to take on effective remediation projects that not only identify the root causes of particular problems, but put comprehensive plans in place to remedy them and communicate those improvements to the FDA effectively.

WHAT IS COMPLIANCE REMEDIATION?

In medical device and pharmaceutical and biopharmaceutical manufacturing, compliance remediation is the process of recognizing problems and creating a plan to correct and prevent those problems from occurring again. Contrary to popular thought, Rodriguez contends that regulatory agencies like the FDA are less concerned with policing manufacturers themselves, and instead, focus on understanding the company's ability to execute internal quality processes *on their own,* and how the company's processes and procedures are used to comply with the respective regulations.

In addition to monitoring sufficient standards for quality, the FDA also works to ensure manufacturers are storing and analyzing quality systems and post market data effectively while creating comprehensive corrective and preventative action plans when quality standards aren't met. When regulatory problems arise, it's up to manufacturers to find effective corrective actions to prevent reoccurrence—that's where remediation comes in. According to Rodriguez, remediation for quality and regulatory compliance typically breaks down into a few essential steps.

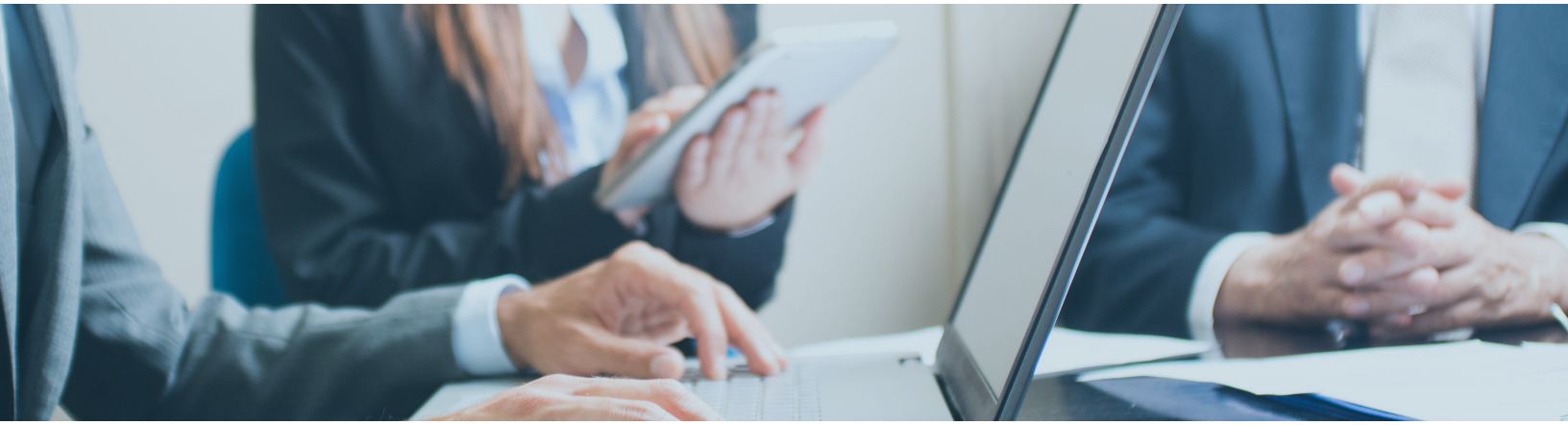
First, a manufacturer analyzes the observations and chooses a quality standards model based on the tasks at hand. Second, an internal investigation is launched with the assistance of qualified experts to assess the affected processes and supply chains to reveal the root causes of the problem. Once these **root causes** are identified, experienced consultants or in-house experts draft a corrective action plan, and submit it to regulators for review. Lastly, the plan is finalized, executed and monitored for effectiveness.

AREAS OF FOCUS BY THE FDA

The FDA focuses their attention on the following compliance streams:

- CAPA
- Complaints
- MDR
- Corrections and Removals
- Design Control
- Change Control
- Management Review
- Production and Process Control

Note that CAPA and Complaints tend to have the most frequent number of findings during an inspection, however, anyone of them are potential areas for deficiencies.



CONTEXTUALIZING OBSERVATIONS AND IDENTIFYING ROOT CAUSES

Drawing on decades spent helping companies solve a variety of regulatory issues, Rodriguez points to understanding the scope of the problem, identifying root causes and implementing effective corrective actions as the three one of the most important goals of remediation in general.

"Effective remediation relies on companies to fully understand and contextualize the observations made during an inspection and address root causes. In order to paint a complete picture of the problems at hand, it's important to gather as much direct feedback from investigator during the inspection as possible."

Once the closeout meeting ends, take the time to analyze each observation with key members of your staff including representatives from Quality Assurance, Regulatory Affairs, Operations and at least one member of senior management. The objective of your analysis should always center around **identifying root causes**, not short-term solutions that only put a Band-Aid on what could be a serious wound.

Getting to the root cause requires thorough investigation. In Rodriguez's view, companies often *"get caught up in the minutiae of a particular observation—addressing only the surface-level components of the problem while ignoring larger threats to quality."* This is especially common in cases where inspectors provide specific examples with their observations. Examples are only meant to provide a means of understanding the effects of a larger problem. Therefore, it's important to view your observations as just the tip of what could be a much larger systemic issue.

GETTING TO THE HEART OF THE PROBLEM

Getting to the bottom of a particular problem can be a difficult task requiring you to string together seemingly unrelated indicators to reveal an underlying issue. When determining what larger problems lie beneath your observations, Rodriguez suggests using the following tips to guide your analysis:

1. Perform a system-wide gap assessment

"In order to get at the root cause of a problem, you'll need to open your entire system up for scrutiny."

Work as a team to gather evidence and formulate conclusions based on what you're able to document and explain in detail. Don't assume any part of your manufacturing or quality system processes are off limits.

2. Realize that observations may be the product of more than one root cause

All too often companies will launch an investigation into a particular process or procedural issue only to stop short of uncovering the full extent of the problem.

"It is critical to understand the scope of the problem. If a problem seems to persist, it's more than likely that whatever was done to correct it didn't completely solve the problem, which means that the true root cause(s) was not identified."

3. Identify all possible solutions to a problem

"While some observations may stem from multiple root causes, it may also be the case that those root causes have a variety of solutions."

Step back and take inventory of all the possible solutions to compare and contrast them in terms of risk, time to implement, and overall effectiveness.

4. Be thorough when defining the problem

"It's next to impossible to find the true cause of a problem if you haven't defined it properly first."

Use the observations as a starting point to distill the real issue at hand before setting out on your investigation into the cause. In most cases a true "gap assessment should be completed" to determine all areas that may also need remediation.

5. Visualize your path to the root.

"Getting to the root cause is a logical progression of looking at problems and tracing the causes until you reach an endpoint".

Create a graph to conceptualize where your investigation is going as you progress.

TAKING GENUINE CORRECTIVE ACTION

Once you're confident you've arrived at the root causes following a thorough analysis of the problems, it's time to craft a corrective action plan. This should explain the steps you'll be taking to fix the problems that were observed, and prevent them from reoccurring in the future.

In addition to the plan itself, regulators will want to know who in your organization is responsible for managing each task along with a timetable they can expect to follow.

"Identify and assign the right resources."

Here are five components found in effective corrective action plans:

1. A clear and concise list of actions

List all interventions you plan to take in order to remedy existing problems through short and long-term corrections and corrective actions, and look at possible global implementations to prevent similar issues in other systems or areas.

2. An explanation of procedural changes

In detail, describe any and all changes to the processes, procedures, or other alterations you're making to the affected systems. In addition to defining what these changes will look like, be sure to include a thorough explanation of how they will affect the accuracy, effectiveness and/or efficiency of the result.

3. Sufficient training resources

Whenever a change is made to regulated manufacturing process, regulators will want to see a clear explanation of any new training needed to ensure your team can follow through with the new procedures.

4. Your action plan

Finally, your remediation and corrective action plans should lay out a set of written procedures describing each of the actions included on your list in complete detail. It is important to map each of the 483 findings to the appropriate corrections, interim controls, root cause(s) corrective and preventive actions. The plans should also include details as to how each of the actions will be verified for effectiveness.

CRAFTING AN APPROPRIATE RESPONSE

Whether you're responding to a Form FDA 483 or warning letter, your response is one of the most important components of the larger remediation project as it's your chance to communicate your corrective and preventative action plan to the FDA. To help guide you through the process, Rodriguez shared ten of the most important elements all responses should include:

1. A statement of intent to comply with the law

"An effective introduction clearly states your organization's intention to comply with all federal regulations."

2. A clear commitment by upper management to remain compliant

"A well-written response not only makes it clear your organization is working to improve, but is committed to adhering to those improvements in the future. When stating your intent to comply with the respective regulations, make it clear that compliance is the top priority among the leadership in your organization."

3. A clear, in-depth analysis of each finding

"Following a clear and concise introduction, it's important to address and analyze each of the findings and/or observations individually. This is key for two reasons. First, it assures the FDA you understand the why the findings were made, and second, it shows your organization has taken the time to assess the observations in full."

4. An explanation of how enhancements will prevent recurrence of the items listed in the Form 483

"This speaks directly to what the FDA is looking for in your response: improvement and enhancement. When explaining the particular actions you're taking to remedy the problems highlighted in the observations, be sure to frame these enhancements by explaining how they will prevent recurrence of the issues in the future. The importance of this point can't be understated."

5. Explain any new training that will support your enhancements

"This is particularly important if the findings identified competence issues within your staff. While it's one thing to explain what your company intends to do to fix something, your enhancements must be supported by a clear explanation of the training that will accompany it."

6. Describe how your company will monitor the progress of your plan

"How you intend to ensure your plan is followed is another important point the FDA will be looking for in your response. After describing your enhancements, take the time to lay out a clear system for monitoring not only that the plan is followed, but also that it's effective."

7. Include any documents that directly support your plan

"While it's important to include any additional documentation that supports your enhancements, don't overwhelm the FDA reviewer with a stack of paperwork. Include only what helps explain the points made in your response."

8. Clarify anything you feel was misrepresented in the observations

"While it's important to include any additional documentation that supports your enhancements, don't overwhelm the inspector FDA reviewer with a stack of paperwork that may be irrelevant. Include only the revised documentation that willwhat helps to explain the points made in your response."

9. Give a reasonable timeframe for action

"Lastly, investigators will want to know exactly when you intend to actually carry out your plan. Be extremely cautious not to overpromise and under deliver. It's far better to give yourself slightly more time than you think you need to make enhancements rather than set unreasonable expectations for yourself."

WHAT TO AVOID IN YOUR RESPONSE

One of the worst mistakes a firm can make in writing its response is demonstrating it either doesn't understand the changes it needs to make or is unwilling to invest the resources to do so. Here are a few common strategies Rodriguez suggests using to avoid when crafting your response:

1. Vague or broad assurances

"It's not enough to simply indicate that "actions have been taken," or "investigations are ongoing." Be sure to describe what is being done, who is doing it and when it will be implemented. It is critical that the company provides objective evidence of all actions taken."

2. Responding rapidly to serious problems

"Submitting a response too quickly can indicate that you didn't take the time necessary to fully investigate the root cause of the problem."

3. Overwhelming investigators with irrelevant data

"Investigators won't be impressed by a mound of meaningless information and will only raise doubts that you're taking the problems seriously."

4. Exaggerating the implications of the changes

"Warning regulators that significant changes will put you out of business or drive away jobs will do nothing to sway investigators. Stay away from these kinds of claims at all times."

5. Responding with a rebuttal

Often, companies will try to justify and rationalize why the observation was not really an issue.

"Refusing to admit a problem exists not only demonstrates an unwillingness to cooperate with federal regulators, but also demonstrates a lack of respect the regulatory system itself, opening yourself up to even greater scrutiny. Never attempt to shift the focus away from the issues in your response. If you don't know what to do, get help from an experienced consultant."

OVERCOMING COMMON CHALLENGES

While each remediation project is unique to the problems a particular manufacturer is facing, large-scale remediation projects tend to present a few challenges common among a variety of applications. Here are two of the more significant:

Treating the symptom rather than the cause

Manufacturers often fail to realize the scope of the remediation necessary to solve systemic problems. Refusing to take on remediation at the scale needed in an effort to save money in the short-term often backfires when rejected responses and subsequent inspections end up costing even more in the long-term.

*"If you're experiencing a product recall, for example, **don't stop at containment.** While it's important to stop shipments of non-compliant products and retrieve defective items from the market, step back and dive deep into your procedures and processes to understand exactly what went wrong. Only then can you can begin to create a corrective action plan that will truly remedy the underlying issues that lead to the recall."*

Misinterpreting the regulations

This is especially relevant for foreign manufacturers who may not be familiar with the regulatory environment in the United States. Compliance to ISO requirements may not be enough.

"While it seems like a given to most, many remediation failures stem from a basic misinterpretation of the regulations themselves. While getting lost in detailed technical language can ultimately lead to trouble, some issues can be as basic as monitoring the inputs of a process instead of the outputs."

THE BENEFITS OF PARTNERING WITH A REMEDIATION EXPERT

One of the biggest challenges of remediation is exposing problems that may be completely unknown to you. Even with a capable in-house team, attempting to uncover systemic issues, and creating a plan to correct them can prove to be a tall order, even for large manufacturers.

"Third party remediation experts offer a fresh perspective while working diligently to perform gap analysis, identify root causes, resolve cGMP and communicate your efforts to regulators effectively."

CONCLUSION

While remediation can seem like an overwhelming endeavor, simply knowing what regulators are looking for can make a huge difference throughout the entire process. While we've covered many of the most important points to consider during remediation, it's important to remember that each situation is unique, and as such, requires a unique approach. This paper is intended to lay a basic foundation for a variety of remediation projects.

We provide expert Quality Assurance consulting services to pharmaceutical, biotechnology, medical device, and dietary supplement companies to help ensure they are in compliance with current business practices and regulations. Our team of auditors can perform a detailed assessment of your existing quality systems and processes, to highlight problem areas and recommend improvements, so that you can build quality systems that are appropriate for your company's stage of development. We can assist you with all aspects of compliance, as they impact your product, including GLP, GMP, QSR, and GCP.

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