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An FDA Warning Letter can be a business disaster. This case study tracks a company from receipt of an FD 483 — that did not find contamination, but only the *potential* for contamination — to 18 months later when the facility received a clean bill of health.

What it did to get there — and what it learned — may keep your site from losing its operating freedom.

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# You Have Failed . . .

## A Case Study in Warning Letter Remediation

*Dear Plant Manager,*

*YOU HAVE FAILED . . .  
to demonstrate the absence  
of penicillin residues  
in your facility generated  
from the adjacent penicillin  
bulk powder manufacturing  
plant, and . . .*

**A** real company received this letter. And similar letters are being sent out frequently. Your company is not immune. Just one line on an FD-483 form and your facility's operating freedom vanishes. In this case study, the potential contaminant is penicillin; next time it could be any biologically active substance. What will you do? Preventing regulatory sanctions and ensuring that your supply chain continues to produce your revenue stream are essential to maintaining and growing the business. In the United States, penicillin contamination is a serious concern: It is a highly sensitizing agent with the potential to cause anaphylactic shock or death — the death knell for any biological product. If you receive a Warning Letter, how do you react to and deal with the agency, with your management, and with your customers?

FDA citations used to be issued only for contamination within your own plant. Now the enforcement bar appears to include possible contamination from neighboring plants. This case study describes the efforts of one group when they faced such a dilemma and how they achieved their objective — lifting the cloud of regulatory sanction and returning “freedom to operate”

to the company. Successful remediation of this kind of citation requires that industry follow a new standard.

### **Setting the Stage**

The story begins with an FDA inspection of a biopharmaceutical plant. The plant being inspected never produced (or handled packages of) penicillin, but a neighboring plant had been in the business of penicillin fermentation for several years. During the inspection, the neighboring plant continued in that business, but subsequently discontinued its penicillin operations.

The FD 483 consisted of over thirty pages of citations that included 47 principal observations, which resulted in the issuance of a Warning Letter with all the associated sanctions. The observations cited other problems as well — validation of multiplant, shared computer systems; equipment and utility validations; and generic quality systems deficiencies among them. These would exacerbate the penicillin remediation process — requiring extensive intracompany coordination between different functional activities — and complicate the communication channels. Compounding the situation further, the manufacturing plant was located in a foreign country, ensuring a multitude of cultural, linguistic, and logistical burdens to overcome as well.

### **Meeting the Challenge**

The original building used for production was dated; initially constructed in 1985, it had several additions and modifications. Capital improvements had been few and consisted mostly of bandage solutions to immediate needs without consideration of the greater future. There were few reliable drawings available that could provide an audit trail of the changes made over the years. A strong QA presence was just being established. For many years, the site was

## Anatomy of an FDA 483

A 1992 memo from the Associate Commissioner for Regulatory Affairs explained to FDA inspectors the process they should use when making observations on an FDA 483.

*As you are well aware, regulatory uniformity has always been a goal in FDA's enforcement strategies and policy, therefore, it is essential that the FDA 483s we issue be understandable, consistent, and contain only significant observations . . .*

*Simply stated, all FDA 483s will adhere to the following general principles:*

- *Observations which [sic] are listed must be significant and correlate to specific regulated products or processes being inspected.*
- *Observations of questionable significance are not to be listed in the FDA 483, but will be discussed with the firm's management so that they understand how uncorrected problems could become a violation. This discussion will be detailed in the EIR.*

*Our FDA 483s must have certain characteristics to be useful and credible documents. These are as follows:*

- *Each observation must be clear and specific.*
- *Each must be significant. Length is not necessarily synonymous with significance.*
- *Observations should not be repetitious.*
- *The worst observations should be listed first.*
- *All copies of the FDA 483 must be legible.*

*Finally, ORA policy requires that inspectional observations will continue to be presented in writing at the close of inspections . . .*

### Reference

- (1) Chesemore, R.G., memorandum "FDA 483 List of Inspectional Observations Policy," 22 July 1992.

provided with QC support only, because the original design had downstream processing that was located at another facility (1). The change in management and leadership from an "upstream chemical" paradigm to a current biopharmaceutical state-of-the-art facility illustrates the growing pains that were also reflected in the staff's difficulty in understanding and anticipating the effect of a regulatory inspection.

The plant staff were numb. Their company produced a real product with a real revenue stream. The possible loss of the U.S. market, and a consequent shutdown, was a potent threat. Setbacks in new product development can touch a company, but halting an existing revenue stream is particularly visible throughout the entire supply chain. Prudently, senior management did not seek to fix blame, choosing instead to address the problems and move forward. Local management was quick to volunteer full support and commit full resources to corrective action, but the problem was finding someone who could lead the efforts to a successful conclusion. As the scope of the damage unfolded, few volunteers were

willing to "place their fingerprints at the scene."

Rescue came from a new QA team — a small, focused leadership group with diverse and complementary skills. The team had experience in coping with negative regulatory situations and in resolving large-scale issues both domestically and internationally. They knew that projects often fail, not because of management skills, but because companies are sometimes unable to adequately control and manage the events that create setbacks. They recognized that the critical factor was to address the observations directly and succinctly. Bemoaning the unfairness of being singled out when there are many other plants similarly situated around the world was not an option.

**Identifying critical needs.** The team identified three primary needs at a conceptual level. First, the team needed to facilitate an open and ongoing rapport with FDA to ensure transparency and mutual respect. That meant clear statements of intent and well-defined objectives so that the company spoke with one voice. All actions needed to be in alignment with regulatory expectations. The

second need was to identify the process requirements that would lead to the required remediation. Many new SOPs, methods, and building modifications would need to be made before achieving satisfactory resolution. The third need required that operating personnel adjust their actions and behaviors to fully benefit from the new working environment and commitment to sustaining the freedom to operate.

Perceptions notwithstanding, the Warning Letter made no accusation of contamination, only failure to ensure against the possibility of contamination. In effect, there was no crime, only inference, but as in the Code Napoleon, guilt had to be affirmatively disproved. There were no ready answers to the observations. All actions, plans, and efforts would center around one objective — operating freedom. The response submitted to the agency was straightforward, nonargumentative, and professional, promising a thorough investigation and substantive corrections. It included a commitment to update the agency frequently with current information and real data. These updates clearly addressed the issues underlying the observations and laid out detailed courses of action with specified timelines for completion.

**Assessing the challenge.** On an operational level, the QA team used a systemic approach based on the GMPs — test and verify — to address FDA concerns about prevention and control. The team focused on four areas where detection and control could be influenced and maintained: environmental monitoring and testing, personnel and material flow, HVAC controls, and finished product testing. Those four areas would meet CGMP expectations and provided a realistic path to success. The information from this multifaceted approach was integrated into a remediation plan to present to site management for consensus and eventually to upper management for approval and funding.

The first action was to verify whether penicillin was even present in or around the plant and if detected, to determine its source. Any penicillin found would need to be localized, contained, and removed. Even if no penicillin was found, future contamination would need to be precluded. No individual had all the requisite skills or depth of knowledge to remediate more than

one or two specific areas, so managing the expertise and input styles into a single coordinated remediation plan was the challenge.

External consultants with selected expertise and experience in one of the four identified areas aided in identifying critical sampling points, detection methods, sample frequency, monitoring programs, and cleaning, removal, and prevention concepts. The use of consultants with recognized competence helped to secure necessary funding from management as well as establishing credibility with the agency. Their expertise was judiciously implemented into the overall plan.

### Developing the Plan

Each of the four areas identified needed to be analyzed for opportunities to improve performance and to meet FDA requirements.

**Monitoring environmental conditions.** The team started by securing baseline data to support future recommendations and decisions. A thorough facility and system review identified all potential contamination threats to the facility and to the processes. This was followed by a risk assessment of the contamination threats to identify critical junctures from which process conditions could be tested and validated. Those data provided the rationale for a long-term monitoring program that could be presented to FDA for feedback. Then the team encountered its first hurdle: Existing test methods were not sensitive enough for environmental monitoring, and the methods being used cross-reacted with product. The challenge was to develop and validate test methods (a swab method for surfaces and a volumetric method for air) that would meet the FDA's standard — six to eight parts per billion.

**Controlling HVAC systems.** A review of the HVAC system was the starting point for investigating airflows, pressure differentials, and isolation. Because the 483 and the Warning Letter specifically mentioned the HVAC systems as a possible route for penicillin contamination, the team had to determine the robustness of those systems. They first identified the requirements expected of a new facility and then challenged their building (already two decades old) against those standards. The gap analysis included not only the HVAC

systems supplying the production areas but those supplying nonproduction and support areas as well (another recommendation received through meeting with FDA and an example of the bar being raised on regulatory expectations).

The results of HVAC analysis indicated at which points resources were needed to ensure that no foreign substances entered the plant. The structure of the final report allowed gaps to be prioritized from critical to less critical in four stages. The priority category was for those areas (such as where open production occurred) that needed to be addressed quickly to relieve the regulatory pressures. Longer range corrections were for less critical situations. Corrective action included ensuring that older systems were redesigned and operated to meet new requirements. The engineering staff wrote user requirement specifications (URS) and commissioned new *as-built* drawings and schematics. Contractors verified and recorded filter integrity, design appropriateness, and the thoroughness of the maintenance programs. The team initiated ductwork integrity tests and maintenance to upgrade controlled areas that required airflow or pattern modifications or other similar changes

### Improving the flow of personnel and materials.

The inspection had pointed out questions relating to personnel and material flow layouts throughout the plant. The team had to address the factory's many entries and exits and the many material flow permutations throughout operations. The number of entrances to the plant was decreased, and controlled zones were established. Visitor controls were tightened, and internal movements were restricted to specific activities.

Personnel training was needed to address the cultural and human side of the FD-483 observations. Inconsistent gowning technique and "self expression" in clothing styles contributed to the analytical difficulties and were ultimately standardized. Significant effort was needed to change long-established habits and practices. Many of the changes met with resistance from personnel, unions, and occasionally even from plant leadership. The plant manager's support and willingness to confront adversity was critical to the success of this effort. A new production support building was identified as a solution to meet

needs, and it was approved. Ground was broken within ten months of receiving the Warning Letter.

**Testing the finished product.** To ensure that all product would leave the building unadulterated, the company made a commitment to the agency to test every product lot. They also tested all lots that were still within their expiration date — more than 400 different batches. Although difficult and costly, this testing became the focal point of concerted effort by an extended intracompany team. They had to establish test methods that were sensitive enough to detect contaminants at the level expected by the agency without product interference. And they accomplished the task. They developed new test methodologies with levels of detection at orders of magnitude below currently available methods. In effect, analytical personnel performed retrospective product analysis at the same time they were doing prestudy testing of three things at once, and at the same time, they were developing methods and validation tests — they built the airplane in flight. It was even more difficult to find a qualified laboratory to perform the testing.

The end result was a comprehensive remediation plan that was accepted by the agency. The key to their success was their frequent communication with the agency. Knowing exactly what concerned the reviewers was instrumental in focusing the remediation because these conversations went beyond what was in code. The team avoided the "false security" trap — taking action on some issues and leaving others unaddressed — that catches some companies. In the end, the agency helped focus the team to be successful.

### Correcting the Problems

Remediation began even before the inspectors walked out of the door. Individuals and management understood their failures and began addressing problems within their purview. The remediation team's objective — restore operating freedom by lifting the Warning Letter — became the objective and set a firm timetable for completion — the date they would invite FDA back for reinspection.

The remediation team defined broad-brush areas and functional responsibilities for each FD-483 observation and identified a

leader, a contractor, or an operating company to meet target dates. By holding specific personnel accountable, action was focused on deliverables in the chain toward success. Regularly scheduled meetings were held in all divisions to celebrate the success of tasks just accomplished or to analyze failures. The meeting then moved forward by charting and assigning the next set of gaps that needed to be completed before the next meeting.

Tasks were clearly defined by precise, measurable activities, such as “Change physical parameter of . . .” or “Get approval signature on . . .” Deficiencies were also precisely conveyed through the simplest means. For instance, the team used digital photos of problems rather than complicated descriptions prone to misinterpretation.

The tag line for the actual remediation could be that of Nike — “Just do it.” Hesitation on a good plan is a waste of personnel, time, and resources. Problems were encountered, and the plan required some adjustment, but with the cooperation enlisted through openness with the agency, these were minor diversions that had little effect on the other areas moving toward the goal.

The conceptual framework was tangible and could be likened to a building project, but the desired outcome was the intangible quality of *compliance*. The milestones were studies, results, analyses, and physical changes. Through open communication and milestone celebrations, building the “compliance” structure became as real to the people involved as if they were building a new plant.

### Reinspecting the Plant

Almost immediately after the original inspection, preparations commenced for the reinspection. Staff shared accountability for the facility’s inspection readiness. The site compliance team created individual binders for each observation so that a complete history could eventually be woven into the plan for that observation.

In a typical GMP operating plant, inspection preparation means cleaning up the plant and tidying up any loose paperwork. In this situation, that wasn’t enough. Despite all the effort toward reinspection, communication was still a visible weakness (See the sidebar

## Communication and Perception in Foreign Plants

Imagine for a moment an American inspector addressing a non-American Engineer in a foreign plant. The inspector asks the question, “Do you test every lot of product before you ship it?” Read that question very literally. Focus on the word “you.”

In a literal translation, there is no indication that the word “you” is plural. Consequently, to the engineer this question might mean, “Do you personally test every lot of product before you ship it?” Although the engineer might find it rather silly that an inspector would ask an engineer if he or she personally tests the product, the polite answer to the question is “No.”

“Communication and Perception in Foreign Plants”). All personnel received inspection training. To ensure that the communication of their efforts would be understood, individuals were asked to prepare presentations of their responsibilities and an overview of a particular system or observation. This was to help them focus their thoughts and to reinforce their self-confidence. American staff played roles and ran simulations in the same rooms intended for the actual inspection. Personnel were encouraged to be forthright about asking for clarification when questions didn’t seem to be associated with sound GMPs. On the reinspection date, the familiarity of the surroundings, the context, and the procedure made it easier for plant personnel to provide clear answers to FDA questions.

### Learning the Lessons

You cannot control the actions of your neighbor. Companies need to protect their supply chains from intentional and unintentional acts. Biotechnology companies became increasingly sensitive to this requirement after the 11 September 2001 terrorist attacks.

Management support in this task is essential. In our example, senior leadership granted the team autonomy and the resources to see the effort through to its conclusion with no interference or micromanagement.

**The agency has specific requirements** that it considers acceptable when it comes to types of sampling, methods of sampling,

The American inspector asked a normal question that in clearer words meant, “Is every lot of product tested at the plant before it is shipped?” The expected answer would be “yes.” With a “no” answer, the inspector thinks that a plant that doesn’t test its product before it is shipped is a plant out of control.

Answers can be misunderstood when common language is used in a location with different cultural or regional communication patterns. In this imaginary scenario, the fact that every product lot has been tested for the past twenty years was never discussed — until it appeared on a formal report.

frequency of sampling, levels of detection, methodologies used, data interpretation, and resampling criteria. These criteria are not always promulgated in code. Unless you meet with the reviewer to discuss in detail your company’s situation, issues, and remediation plans, there is a high probability that you will spend significant time, energy, and money going in the wrong direction. Even best intentions and self-assured consultants can put you on a fast track in the wrong direction.

**Build a legal case.** Use project management concepts that transcend cultural and communication barriers. In multinational companies, remember that it is not your country and not your culture. The language of logic, however, is universal. Recognizing and being able to communicate the problem is difficult and is the first step to remediation. It is critical to ensure your solutions are compatible with FDA’s statement of the problem. To ensure agency and management acceptance, use a legal model — build a case just as you would in a lawsuit — and use the evidence to support your contention. You cannot push a rope, you need to pull it. Create a chain of custody for each activity, and use it as a road map. Define roles clearly, remembering that some people are coaches; some are players.

**Look for solutions, not blame.** The immediate reaction to a threat is to react negatively, whether against a group or an individual. It

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is easy for anger and despair to manifest as blame. Successful resolution, however, requires that everyone look to that success and see what their part might be in achieving it. The past is history and cannot be changed. The future is determined by each person's actions as they relate to each other and the world.

In every crisis, there are clear-headed people who accomplish the tasks required to resolve the challenges. There are few times in our lives when our individual contribution can make such a difference in so many other's lives. Be confident of success. A team of "winners" is contagious — and no one wants to let down a winning team. The seemingly impossible is manageable. It just requires careful and deliberate action.

**Epilogue**

Twenty-four months after the original inspection, FDA forwarded an Establishment Inspection Report (EIR) that formally lifted the warning letter and returned its freedom to operate to the factory.

**Reference**

- (1) Arling, E.R., Dillon, R., and Noferi, J., "Creating Effective Biopharmaceutical QA/QC Organizations: Your People Are the Key," *BioPharm* 15(6), 40–46 (June 2002). **BPI**