



## Making a comeback after a negative experience with the US FDA



Glenn Neuman

Negative feedback from the FDA does not necessarily mean disaster. Glenn Neuman, director of scientific affairs at New World Regulatory Solutions, gives advice on how to get a company back on its feet after a knock-back

Nothing can take the wind out of your sails like a negative FDA experience. You pour your heart and soul into your quality system, or your FDA submission, or your PowerPoint presentation and rehearse for a face-to-face meeting. You are convinced that you have a winning package that will showcase your quality system or the health benefits of your technology. The meeting is going well, and the agency appears to be open and receptive to your ideas and execution. Then, the

taste of success suddenly turns sour from a single question or comment. You can hear the cosmic “click” as the agency digs in its heels. Your collar becomes too tight, your throat becomes parched, and true to the textbook description of an initial reaction to bad news, you experience denial, followed by anger. You try to hide the incredulous expression that has crossed your face, but it’s too late. The opposition has locked arms, and they know they’ve got you. You bite your tongue to prevent yourself from

stammering an unintelligible or damaging response. You pray for a breeze strong enough to move you forward, but you are dead in the water and the current is against you. You’ve had a negative FDA experience. And when it’s all over, you huddle with your colleagues to plan the next steps.

Negative FDA experiences come in all sizes, but in the most general terms, either your plans or your operating system has been shot down. The agency’s personnel are masters in giving negative feedback,

and they are adept at handling attempts to countermand their position.

Contrary to what one might think, the FDA does not enjoy dealing in disappointment. But it does take pride in its roles of cop and judge when it has protected the public from a looming threat (which, after all, is its charter), or when it feels that it has saved a sponsor from a fruitless endeavour by panning a weak pre-IDE. And when the cheaters get caught, we can all be thankful; those who do not play by the rules should not be allowed membership of the device community.

For the past year, the promise of change has been a consistent theme in FDA announcements, and we should brace for tougher standards in both submissions and compliance. The policy changes that will be forthcoming from the FDA coincide with changes happening within. Some FDA veterans have left while others have relocated within the agency. The Center for Devices and Radiological Health (CDRH) appears to be rebuilding from within, bringing in rookies, launching new initiatives, and planning for growth. There are new faces in upper management and on the review staff, which has grown.

While fresh eyes can better find old flaws, it takes a few years for a new reviewer to master the game, and during that time some frustration can be expected on both sides of the regulatory gate. If faced with an unprecedented requirement or a contrary comment from a new reviewer, the industry veteran will take a tactful approach, citing historical outcomes and employing patience to avoid a negative experience. The industry rookie might not have those countermoves in his or her arsenal. However, migration of staff within the FDA can lead to the agency employing a mixture of tactics, begetting unprecedented requirements that cannot be countered. For example, should a reviewer from CBER (biologics) join OIVD (in vitro diagnostics), bringing in his stricter CBER review standards, OIVD might begin asking for data from multiple lots in 510(k) submissions, where one lot was previously the norm. And when new requirements arise from new thinking or the mending of old flaws, industry will have no choice but to adjust and comply.

In the compliance arena, the FDA expects to send out more 483 post-inspection and warning letters this year than were issued last year. I have not heard predictions of more submissions to the FDA, or of more manufacturers coming on-line. Thus, an increase in the rate of

negative FDA experiences can be expected.

Depending on whether you are confronting a submission problem or a compliance issue, different requirements are exacted and different comeback strategies are needed. Compliance infractions are enforced by the Office of Regulatory Affairs (field actions and inspections), or the Office of Compliance within CDRH or CBER. Enforcement – the operative word here – is based on risk; though minor observations can be addressed with a lick and a promise, major rifts are punishable by fines, seizures, injunctions, and even jail. For the most egregious of them, the courts will decide your comeback, but the FDA will give you several warning shots across the bow before sinking your ship.

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## When the bottom line is threatened, there can be internal pressure to take aggressive action with the FDA, but aggression and arguing won't work. Politely presented creative and constructive solutions are better

Similarly, negative feedback on your FDA submission is typically heralded by a series of real-time interactions with the reviewer. You will be given an opportunity to respond to requests for additional information within a prescribed time frame. The nature of the request and your ability to respond in time can be predictive of the final outcome for your submission.

### Coming back from negative FDA feedback on your submission

Submission reviews at the FDA are based on scientific evidence. Of course there are binding regulatory requirements that must be met, but those are straightforward and unambiguous for those who are familiar with them. Scientific evidence, however, must be interpreted clinically and statistically using a risk/benefit approach to gauge safety and efficacy. Needless to say, the conclusions of a scientific review drawn by the sponsor and the FDA can differ. Having a submission fail from a seemingly unscientific and unjustified interpretation

of the data is frustrating. The reviewer might conclude that the studies do not support the product claims, or that it is not possible to extract the information needed because of how the data were presented. While the opportunity to submit more or reorganised data will likely be extended, the time delay and the cost of additional studies will have a negative impact on the bottom line. If the amount of additional information requested is very large, then your comeback plans will have to include a cost/benefit business analysis.

At this point, when the bottom line is threatened, there can be internal pressure to take aggressive action with the FDA. Aggression and arguing won't work. Your bottom line is not the FDA's business, and it doesn't want to hear about it. Politely presented creative and constructive solutions are better. Avoid the temptation to go over the reviewer's head – follow the chain of command. Each department within the agency works as a unit, and the supervisors will protect their staff. Remember that you are fostering a long-term relationship with the reviewer and his or her colleagues. We have heard from too many companies that their relationship with the FDA is "strained," and it becomes a limiting factor in their operations.

With apologies for the cliché, the best comeback for a crippled submission is to avoid it in the first place. Pre-IDEs are strongly encouraged by the agency, where the study plan is reviewed beforehand and a non-binding agreement is reached. Pre-IDEs are also intended to prime the pump so the submission will flow through the review process with less impedance. They eat up 60 to 90 days of phase 0 time, but they significantly reduce risk, and with the promise of imminent change in the review criteria, a Pre-IDE is strongly recommended. Also, with "predicate creep" in their sights, FDA may have a critical view of what you propose as a predicate device for a 510(k), and that's something you definitely need to know beforehand. The best part is that Pre-IDEs are free – the agency does not charge for reviewing them.

Aside from the data review, design control, risk analysis and software validation are common areas where deficiencies are cited. The FDA has excellent guidance for devices that include software, and following it, with the help of your software engineers, will circumvent software review problems. Design control and risk are inexorably linked in the quality system, and weaknesses uncovered in these areas of a submission can tip off inspectors that quality system deficiencies might exist.

## Coming back from negative FDA observations about your QS

FDA inspectors, with their deadpan formality, are trained to find non-compliance. Their mere appearance at your door is considered by many to be a negative experience. If you receive a 483 or warning letter, then responses to the FDA are required, so the comeback process includes proper FDA etiquette.

A company is well-advised to have formal procedures in place for handling an FDA inspection. Staff should be trained in appropriate behaviour during an inspection. Procedures should include having a designated place for the FDA inspector to occupy during the inspection. You can offer the inspector a (non-alcoholic) drink or a snack, but in my experience, they will refuse anything but directions to the restroom. Have an individual from your company sit with the inspector (no, not in the restroom), and have another individual be designated as the “runner” who will go and fetch any requested documentation.

The inspector will likely take some of your documentation with them when they leave. Keep a designated copy of everything they take, so you have an exact duplicate record of what is in their possession.

## During an FDA inspection, answer only the question that is asked, and do not embellish

Of course, you cannot restrict the inspectors' presence to the interrogation room. They may walk the floor of your manufacturing facility, and they may speak with employees. This is where employee training is crucial. Answer only the question that is asked, and do not embellish. My favourite example is, if the FDA inspector asks, “Do you have the time?” you answer “Yes” but you do not then follow up with the time shown on your wristwatch. If the time on your watch is different from the time on the inspector's watch, you may have opened Pandora's Box. Wait until the inspector asks specifically for your record of the time, and then send the runner to get it.

It might be possible to avoid some 483 findings during the inspection. The inspectors will reveal their findings as they go, and present them in the wrap-

### Figure 1

**1. Be (or at least act) thankful.** The FDA views its role as assistive, not adversarial, especially if you indicate your intention to comply. For example, view a 483 notice as an opportunity for improvement (see *Don't panic if you receive a 483 inspection letter*, [www.clinica.co.uk](http://www.clinica.co.uk), 5 March 2010). No matter how bad the news, there is a comeback route. Work with the FDA to get a satisfactory resolution, because it wants to work with you.

**2. Be responsive.** Respond by the deadline and keep to the point. Do not offer more information than was requested, because that can invite further investigation. The FDA always reserves a caveat that its listed observations might not be complete. But do be thorough in your response to the inspectors' observations, and the issue will be closed sooner. Do not argue, but frame any objections you have in the form of questions or proposals. The goal is to get this behind you as soon as possible.

**3. Be professional and tactful.** It is possible to make bad things worse, and your plan and response should be reviewed by someone with experience in FDA matters. If you are new to the scenario, bring in outside help, but use your vendor qualification procedures to ensure that any consultant you retain is qualified. If you have seasoned staff on board, let them handle the issues.

**4. Be credible.** Be sure to follow up on any promises made, in a timely manner. At their next opportunity, the FDA will verify that you have followed through on your plan of action.

**5. Initiate a corrective and preventive action (CAPA) procedure.** There was something wrong, so it needs to be corrected, and measures must be put in place to prevent recurrence of the problem. Identify the root cause and fix it. If faulty execution is the root cause, training might be needed, and that training must be documented. The FDA inspectors will look for this CAPA on their next visit. They will be looking for the effectiveness of your CAPA, so be sure that objective effectiveness metrics are included in your CAPA procedures.

**6. Reassure.** Customers, shareholders and other stakeholders will need to know that you have the situation under control.

up meetings at the end of each day. Here you may have an opportunity to clarify an inspector's misconception, or to correct a minor issue on the spot. If it's a warning letter you are dealing with, then your comeback will include at least a partial overhaul of your quality system.

### Smooth sailing

Figure 1 is a six-pack of help for anyone needing to get back on track after having their quality system derailed by an FDA inspector.

The comeback must be effectively orchestrated for customers, investors, and for the FDA. If you have had a negative experience with the FDA, then it has had a negative experience with you. We hear of the woefully deficient submissions and how they consume valuable FDA resources. We read about the enforcement actions, often with disbelief about the brazen disregard for the regulations that triggered them. Regulatory and Quality Affairs is the kingpin of the device industry, because without it, no matter how great the technology or how skilled the sales and marketing team, you have nothing to market. Getting back on course and staying there requires experienced and skilful navigating through the regulatory waters.

It is said, “To err is human, but to forgive is divine.” The FDA is human. Winning back the confidence of the FDA can be more difficult than keeping the confidence of your customers and investors. Your customers need you, because your products are validated and entrenched in their system. Your investors are aware that the course can be wavy, especially during a storm. But the FDA has all the grisly details of your deficiencies, which are not available to the rest of the world. The FDA has a memory, and the reviewers talk with the inspectors. While they pledge to move forward on fresh tracks, their negative experiences with a company, and the people responsible for them, remain in their collective memory for a long time. It will take a few consecutive sterling performances to win back the FDA's confidence, and that's the best long term course to take for a successful and permanent comeback.

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