The FDA 483

by Carl Anderson

Sitting in the 17th floor conference room, I had an unobstructed view of the dreary industrial suburb of one of Europe’s uglier cities. The corporate counsel was definitely not pleased. “I was hoping that we would be avoiding an enforcement action,” he said. I explained that the form FDA 483, Inspectional Observations, did not represent an enforcement action by the Food and Drug Administration. It only represented the preliminary observations of the FDA field investigator (or Consumer Safety Officer- CSO).

Along with the IRS 1040, the FDA 483 is one of the most feared pieces of paper in the government’s arsenal. It is also one of the most controversial and misunderstood. Now, after over 50 years in existence, the “483” is going through two distinct changes. The first is designed to inform the recipient that it is indeed a preliminary finding of the FDA CSO. The second is the profound change caused by “Turbo EIR.”

A look back. First, let’s look at what the 483 was originally intended to be. After World War II, many firms complained that FDA enforcement actions took place without warning. In those days food establishments, many of which were quite small, represented the vast majority of FDA’s inspectional work. In fact, in the majority of FDA’s 20 districts food still represents the largest program area. FDA had three primary weapons to “enforce the Act:” seizures, injunctions, and prosecutions. A typical inspection would be a food sanitation inspection. An FDA inspector would conduct an inspection, collect samples and exhibits to support adverse findings, and write an establishment inspection report (EIR). The samples would be analyzed in the district laboratory and the laboratory worksheets, along with the EIR and exhibits, would be sent to the district’s compliance branch for regulatory review. If the district determined that an enforcement action was necessary, they would then proceed to the courts seeking a seizure, injunction, or prosecution. The firms would have little advance notice of the Agency’s intentions.

For this reason FDA developed several tools to inform regulated industry that it had found deficiencies and might proceed with regulatory action. The tools included the “NAF letter” or Notice of Adverse Findings, which no longer is used. They also include the 483 and Warning Letter. The Warning Letter was originally intended to be just that, a letter warning the firm to take corrective actions or face regulatory action including the possibility of a seizure, injunction, or prosecution. In the case of a serious violation the Agency would not issue a Warning Letter but proceeded straight to an enforcement action.

Things have changed. Today, many inspections are quite different from a dirty food warehouse. They include inspections in the bioresearch monitoring program for clinical investigators, Institutional Review Boards (IRBs), sponsors/monitors of clinical research, and GLP laboratories that really have no product to seize. Injunctions and prosecutions have become rare and are only used in the most serious cases. Other enforcement tools such as debarment and clinical holds are now used for serious cases in the bioresearch monitoring program. And Warning Letters and the 483 have taken on a whole new meaning. For many firms, they are the enforcement action.

This is the reason for the first change. Today, each FDA 483 contains a statement at the beginning of the document explaining that the citations on the 483 “are inspectional observations, and do not represent a final agency determination of your compliance” (see “Important Tip” for full wording). This change took place after the FDA 483, Notice of Inspection, was given an addendum, a “page 2,” that listed offices firms could contact within the Agency if there was a disagreement with the CSO. However, neither change really altered the dynamic during an inspection. Few firms contact the district office during an inspection and no one likes to receive a 483 regardless of any disclaimers the Agency may place on the form.

The world according to Turbo. The biggest change to the 483 since its inception is the institution of “Turbo EIR.” This really is a profound change in the way an FDA CSO conducts an inspection. Each CSO is supplied with a laptop computer and printer. The laptop is loaded with “Turbo,” an automated FDA 483 and EIR reporting system that has “canned” citations for every 483 observation. It took several years to implement but now every program area has 483 citations that the CSO is required to use. There is no way for the CSO to override Turbo and every 483 issued must use the Turbo wording. The program should probably have been named “Turbo 483” because it is the canned 483 citations that drive the entire process.

ABOUT THE AUTHOR

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Throughout my career at FDA I was told that nothing belonged on a 483 except “clear and significant violations of the regulations.” However, determining what was “clear and significant” has been a topic of constant debate and quite a cottage industry for lawyers and consultants. FDA received steady criticism that many 483 observations were trivial and weren’t consistent between different districts and CSOs. Frequently the criticism had merit. So the Office of Regulatory Affairs, the Agency’s field organization, came up with Turbo EIR to quell criticism, pursue uniformity, and develop a database of EIRs and inspectional findings.

Here’s how it works. Let’s say that during an FDA inspection of a drug manufacturer the CSO notices that a mixer was not cleaned between batches and there is caked product from a previous batch on the mixer. This is a clear and significant violation of 21 CFR 211.67(a), Equipment cleaning and maintenance. The CSO makes a notation in the regulatory notes and takes a photograph of the mixer (yes, photographs are legal). At the conclusion of the inspection the CSO opens up Turbo EIR and searches through the drug GMP citations for the appropriate citation for the mixer. The CSO clicks on the citation “Equipment and utensils are not cleaned at appropriate intervals to prevent contamination that would alter the safety, identity, strength, quality or purity of the drug product. Specifically,” and proceeds to type in the specifics of the mixer.

The word, “specifically” divides the citation in half. Everything before “specifically” is boilerplate language, provided by Agency CFR experts. Everything after “specifically” is written by the CSO. The CSO then prints and issues the 483 to the firm. The CSO is instructed to inform the firm at the exit interview that “the conditions listed may, after further review by the Agency, be considered to be violations of the Food, Drug and Cosmetic Act. Legal sanctions, including seizure, injunction, civil money penalties and prosecution, are available to FDA if establishments do not voluntarily correct serious conditions.” (Investigations Operations Manual)

When the CSOs return to the local FDA office, they connect to the Turbo EIR server, and their 483s are downloaded and available for the CSOs’ supervisors, and every other FDA employee, to review. This has obvious benefits for producing consistent 483s, for program managers’ ability to access necessary data, and for the individual CSO to learn what other field investigators are finding during their inspections.

Not quite ready for prime time? Many feel that there are flies in the ointment. Let’s see why. During a clinical investigator inspection the CSO may find that a study coordinator failed to place over-the-counter analgesics on the study in accordance with the investigational plan. That’s a big deal. The consistent failure to report concomitant medications belongs on a 483.

In the past, a CSO might phrase this citation in the following manner: “For 7 of 15 charts reviewed, concomitant medications were not reported in the case report forms as required by the protocol. Specifically, ...” This places the violation in the proper perspective. It directly addresses the issue of concomitant medications right up front and references the protocol, which is the regulatory requirement that was violated. However, now a CSO is required to use the Turbo citation, which can sound much more serious. The citations almost always paraphrase the regulations. This citation begins, “An investigation was not conducted in accordance with the investigational plan, specifically,” Whooa, wait just a minute. Does the failure to report some aspirin and ibuprofen constitute “not conducting the study in accordance with the investigational plan”? Isn’t that a little harsh? And that’s exactly the objection that I have heard from several industry professionals. You know, they just may have a point.

Another criticism is that CSOs are trying to fit round pegs into square holes. Because the wording in the Turbo citations is different from the day-to-day realities of an inspection, CSOs have had difficulties finding the right citation to use.

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Critics say this has two negative impacts. First, the wrong citations are being used and thus the 483s don’t always make sense. Second, there are fewer 483s being written because of the difficulties in using Turbo and firms that should receive a 483 aren’t. These problems suggest that there needs to be more discussion inside and outside the Agency on what constitutes a legitimate inspectional observation and how it should be cited on the 483. As always, improved communication between Agency management, CSOs, and regulated industry is the key to resolving compliance issues.

Despite these difficulties Turbo EIR has many positive features. Hopefully, firms will get used to the new language. At the same time FDA needs to review the impact of Turbo EIR, listen to legitimate criticism, and make the changes necessary for the new system to work effectively. In particular the CSO needs training in more than the mechanics of Turbo EIR. Training is also necessary in identifying violations, determining significance, and referencing the appropriate regulation in the CFR for the violation.

Key Tips for a Smooth Inspection Process

• Be clear from the very beginning what type of inspection the FDA CSO (Consumer Safety Officer) is conducting. Research the compliance program guidance manual (CPGM) and the regulations for the specific inspection the field investigator will be conducting. Become familiar with the regulations for your product area. Regulations are available at: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm.

• The CPGM are available at: http://www.fda.gov/ora/cpgm/default.htm.

• Communicate daily with the CSO on what he or she is finding during the inspection. Try to make corrections on-the-spot, when possible. However, do not make rushed corrections that are inadequate. It is better to state what corrections you will make and give a time frame.

• If you receive an FDA 483, discuss the observations with the FDA CSO so you understand what the CSO intended for each 483 item. This communication is emphasized by the Agency to the CSO; take advantage of this to avoid misunderstandings.

• When you receive a 483, inform the CSO that you will respond in writing and ask that they include that information in their report. That will inform supervisors and compliance officers reviewing the report that a written response should be expected.

• Always respond in writing to an FDA 483. If you have a valid objection, state it in a deliberate, professional manner. Write the response promptly, within one to two weeks. However, it is not necessary to submit the letter immediately after the inspection. Usually there will be a few days at the minimum before the CSO writes the Establishment Inspection Report (EIR). Take an extra day, and a few deep breaths, to make sure the letter is written in an objective, cooperative tone. Remember, if you make trivial objections to 483 items, you lessen the impact of the entire letter.

• When making corrective actions, always give a time frame in your response. Corrections should be prompt, within 30 days, unless there is a valid reason for a delay. Attach any documents that show your corrective actions such as SOPs or memos written to staff.