The FDA-483: History and Use in Drug Inspections

Dale Cooper

_PDA J Pharm Sci and Tech_ 1996, 50 386-390
COMMENTARY

The FDA-483: History and Use in Drug Inspections

DALE COOPER

Kensington, California

Introduction

Almost everyone involved in pharmaceutical manufacturing knows that Food and Drug Administration (FDA) investigators are required to issue a written list of deviations from Current Good Manufacturing Practice (CGMP) at the conclusion of drug inspections. They also know that this listing is made on a government form called the FDA-483. But far fewer people know that the requirement to issue this form simply represents FDA policy rather than a legal requirement. FDA adopted this policy to assist firms in voluntarily complying with GMP requirements; not to provide the investigator with a punitive tool. Given the intent of this policy, it is unfortunate that many people in industry and even a few in FDA have an inadequate understanding of the purpose of the FDA-483, its limitations, and the regulatory context in which it exists. This situation causes problems for industry and FDA.

In 1978 and again in 1979 articles appeared in this journal by FDA employees discussing FDA policy and FDA procedures related to the issuance of the FDA-483 (1, 2). These articles attempted to correct many of the misunderstandings then current in the drug industry about its use. Many of these misunderstandings have persisted. But before once again directly addressing these misunderstandings and related problems, it will be useful to a more complete understanding of the FDA-483 to look in some detail at its history.

Legislative History

From time to time, FDA speakers tell complaining drug industry groups that the creation of the FDA-483 was not FDA's idea, but that of industry. Those speakers are correct, although somewhat misleading in their attribution. The industry that asked for a written list of inspectional observations was the food processing industry, primarily midwestern tomato canners. The drug industry had virtually no interest in establishing such a requirement.

In December 1952, FDA lost the inspectional authority given to it by Section 704 of the 1938 Federal Food, Drug and Cosmetic Act. FDA had prosecuted the president of a Washington state apple processing firm for refusing to permit entry or inspection. The company appealed the fine, and the case went to the U.S. Supreme Court. Section 704 was further amended to include a new section, 704(b), that required the FDA officer or employee making an inspection to issue a written report upon completion of an inspection setting forth “...any conditions or practices observed by him which, in his judgement, indicate that any food, drug, device, or cosmetic in such establishment (1) consists in whole or in part of any filthy, putrid, or decomposed substance, or (2) has been prepared, packed, or held under insanitary conditions whereby it may have become contaminated, or whereby it may have been rendered injurious to health.” In 1953, FDA created the FD-483 “List of Observations” form on which these observations were to be recorded.

In the hearings held by the House Committee On Interstate and Foreign Commerce that resulted in these new requirements, allegations were made by some elements of the food industry that inspectors often entered plants without properly notifying management. Some industry members accused FDA inspectors of sneaking in through the back door or even breaking and entering. For the midwest tomato canners, these sins were compounded by the failure of inspectors to fully inform them of conditions they considered to be objectionable. At best, so the testimony went, the inspectors would give a brief oral summary of what they observed without indicating that anything in particular was seriously wrong. The tomato canners, not being properly informed by FDA inspectors, innocently shipped their products out of the state only to be surprised by federal seizures of interstate shipments in which mold or insect contamination was charged. In other words, these tomato canners felt that FDA inspectors were setting them up for seizure actions of interstate shipments rather than warning them at the end of an inspection of real problems they needed to correct. They wanted legislation that would...
require FDA inspectors to issue a written report to management listing objectionable conditions at the end of inspections so that they could take corrective action and not ship food FDA considered to be adulterated with filth.

Charles W. Crawford, Commissioner, Food and Drug Administration, had other views. He testified that it was standard practice for FDA inspectors to identify themselves and show credentials at the beginning of an inspection. He also said that it was standard practice for the inspectors to orally inform management of unsatisfactory conditions before leaving a plant. He thought that this process had worked well. In a prepared statement he said "In 45 years of enforcement there has been no significant desire expressed by any industry for inspectors to leave written statements of objectionable conditions with the plant management, except in the case of grain-elevator operators and tomato canners. The elevator checklist was put into effect more than a year ago. We intend to extend this procedure to other industries to the extent that voluntary compliance may be promoted or that it may be advantageous to enforcement."

He also said that in the late 1920s "The Administration...adopted the practice of supplementing oral warning given by inspectors of objectionable conditions they observed in factories with written warnings on violations generally, except those of the most serious or deliberate character. It became evident after a few years that many manufacturers were not troubling themselves to correct illegal conditions until they received a warning." This policy was discontinued because it "...encouraged avoidance of the responsibility placed on the manufacturer by law, because it was tending to shift that responsibility to the Government, and because it was thus lowering the degree of voluntary compliance...." In other testimony Commissioner Crawford expressed his concern that leaving a written report covering deliberate violations would interfere with effective enforcement. From the context of his testimony, his concern seems to have included deliberate economic violations such as adulteration of food by adding undeclared fillers, e.g., water to juice. However, other than this later concern, Commissioner Crawford offered little if any opposition to the proposal to require that a written report of objectionable conditions be issued to management at the end of inspections (S).

As for the drug industry, they had little interest in a requirement for any kind of report. Although they supported the reestablishment of FDA's inspec­tional authority, their overriding concern during the hearings was to make sure that the authorized scope of the inspection was not expanded in the process. Two series of quotes illustrate this lack of interest quite well.

Dr. Frederick J. Cullen, representing the Proprietary Association, is being questioned by Congressman John V. Beamer, Indiana.

Beamer: "I would like to ask a question that has repeatedly been asked. Would you see any objection to ask that the inspector leave a copy of his report with the manufacturer?"

Cullen: "I would like to answer that from the standpoint of the drug industry, I cannot see where the report of the factory inspection that is made by the inspector would do a drug manufacturer very much good, for this reason. The inspector can look at the equipment, look at the plant, and determine about sanitation. If the plant manager is any type of man at all, he knows that already. If the boss of the place is on the job, the place is already clean." "Going back to the raw materials in the crude drugs, they might give some information there as to the conditions of the warehouses." (6).

Leslie D. Harrop, general counsel, American Drug Manufacturers Association and president and general counsel of the Upjohn Co., is being questioned by Congressman Orin H. Harris, Arkansas.

Harris: "What would be the reaction to a requirement for the inspector to file a copy of the report after the inspection?"

Harrop: "I think I would feel the same as Dr. Cullen does about that. It would not mean much to the pharmaceutical manufacturer. I do not know for the food industry whether it would be valuable for them." "I think it might be, but I am not qualified to speak in that field. We do not see any need for it. They are never very reticent in telling us what they think about the situation. We do not have any difficulty ascertaining that." (7).

From the record, it is clear that the primary congressional concern in 1953 centered on the reporting of insanitary conditions observed by FDA inspectors during the inspection of food establishments. However, without any direct industry objection, the reporting requirement was logically extended to cover drugs, devices and cosmetics as well as foods. The wording of the reportable conditions under 704(b) follows almost word for word sections 402(a)(3) and 402(a)(4); sections 501(a)(1) and 501(a)(2); and sections 601(b) and 601(c) of the 1938 Act which respectively describe insanitary types of adulteration of foods; drugs and devices; and cosmetics. Other types of adulteration described by the act, e.g., that of an economic nature, were not included.

But in 1953 there was no legal requirement that drug firms conform to "good manufacturing practice" and, therefore, whether GMP deviations should be reported was not an issue. However, on June 15, 1960, Senator Kefauver introduced Senate Bill S.3677 that provided for, among other things, the licensing of persons (firms) engaged in the production of prescription drugs. This requirement was intended to ensure the quality of drugs, particularly generic drugs. Then, on July 2, 1960, Senator Hill and Representative Harris introduced identical bills, S.3815 and H.R. 12949 respectively. These bills countered Senator Kefauver's licensing requirement with one for adequate controls (the term "good manufacturing practice" was used later) in the manufacture of all drugs; not just prescription drugs. Section 501(a)(2)(B) was added to expand the adulteration provisions of the Act to include those drugs not meeting this new requirement. These bills also amended section 704(b). They required inspectors to report observations indicating that a drug "...has been or is being manufactured, processed, packed, or held under conditions which may cause such drug to be adulterated within the meaning of section 501(a)(2)(B)." However, this amendment of 704(b) was dropped from the final legislation that emerged in 1962 as the Kefauver/Harris Drug Amendments.

History of FDA's Development and Use of the FDA-483

After passage of The Factory Inspection Amendments of 1953 in August, inspectors began writing their inspectional observations of insanitary conditions on blank sheets of paper and addressing them to the inspected firm to meet the new requirement of section 704(b). The first edition of the FD-483 was issued later that year (8).

With the passage of the 1962 Drug Amendments producers of all drugs, both finished dosage forms and bulk drug substances were required to comply with GMPs. For a relatively short period of time after the CGMP regulations became effective in June, 1963, FDA issued FD-483s for
the use of FD-483s implied that insanitary conditions had been found rather than GMP deviations. They also correctly pointed out that issuing a written list of observations of GMP deviations was not required by section 704(b) of the Act. FDA responded by directing that no FD-483s should be issued to drug firms. But in 1966 FDA told the district offices that they could be issued for insanitary conditions. Until late in 1968, FDA investigators only covered their observations of GMP deviations orally at the end of an inspection.

In 1968, FDA determined that, although the CGMP regulations had been in effect for five years, the drug industry, as a whole, was not in compliance. To remedy the problem, FDA decided to inspect the drug industry into compliance. The program FDA developed was the unprecedented and ambitious “Intensified Drug Inspection Program” (IDIP). All domestic prescription drug manufacturers were to be inspected. All dosage forms were to be covered. The inspectors were required to witness all production and control operations. And, most importantly, the inspections were to continue until complete voluntary correction was achieved. If firms were not willing or able to voluntarily correct GMP deviations, correction would be achieved through regulatory action. Given the anticipated length and in-depth coverage of these inspections, FDA and the drug industry recognized the practical necessity of periodically giving the firms a written list of GMP deviations. (Some of these inspections did, in fact, take a year to complete.) After first ruling out the use of the FD-483 because of industry opposition, an alternate method of reporting observations to drug firms was developed: the “FD-2275 DRUG INSPECTIONAL OBSERVATIONS.” This was a simple yellow form upon which the inspector listed CGMP deviations and all other objectionable conditions. No legal requirement to issue the form was cited nor was any reason for its issuance provided on the form. The FD-2275 was used to report inspectional observations made in all domestic, non-biologic, drug inspections from October, 1968 until November, 1975 (9).

In 1975, as part of FDA’s effort to consolidate procedures, eliminate paperwork, and reduce the number of forms, the FD-2275 and the FD-483 were combined into a new FD-483. The former title, “LIST OF OBSERVATIONS,” was changed to “INSPECTIONAL OBSERVATIONS.” Added to the old printed reference to Section 704(b) of the Act on the back of the form was a new reason for issuance: “To assist firms inspected in complying with the Acts and regulations enforced by the Food and Drug Administration.” This is the only reason given that is applicable to GMP deviations. At the bottom of the page on the front side of the FD-483 was the statement: “REPLACES FD-2275 AND PREVIOUS EDITIONS OF FD-483.” This statement appeared on the July, 1975 edition of the form, but was omitted from the next edition that was issued in 1978. (In 1978, the FD-483 designation was changed to FDA-483.)

The use of the new FD-483 became mandatory on November 3, 1975 (10). This also signaled an important change in FDA policy affecting foreign firms. The new form was to be used on overseas inspections. Prior to this time foreign firms had only received oral reviews of GMP deviations from investigators (formerly known as inspectors). It also marked the first use of the FD-483 in FDA inspections of biologic establishments.

The FDA-483 in use today has only undergone minor changes since 1975.

**Issuance and Content of the FDA-483**

FDA’s policy covering the issuance and content of the FDA-483 has remained fairly constant over recent years. However, from time to time, FDA sees the need to make a strong restatement of that policy to the field organization. In a July 22, 1992 memorandum to Regional Food and Drug Directors, District Directors, and Investigations Branch Directors the Associate Commissioner for Regulatory Affairs (ACRA) concisely reiterated the basic long-standing policy. Its main points are quoted below.

“Observations which 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” (EIR is the establishment inspection report).

“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 repetitive. The worst observations should be listed first.”

Since 1954, FDA has provided detailed guidance for the issuance of FDA-483s in a manual first called the “Inspectors Manual,” then the “Inspector Operations Manual,” and finally the “Investigations Operations Manual” or “IOM.” The points quoted above are also strongly made in the current (1994) IOM under Section 512 “Reports of Observations.” Reviewing this section will reveal that in addition to CGMP deviations there are many other reportable observations on this form that are not required by Section 704(b) of the Act. All of these are made, as the FDA-483 explicitly states: “To assist firms inspected in complying with the Acts and regulations enforced by the Food and Drug Administration.”

For foreign firms the policy governing the issuance of FDA-483s is different. In 1994, FDA revised its “Foreign Inspection Manual.” One of the revisions called for listing conditions that normally would not appear on a FDA-483 issued to a domestic firm. Such conditions would be those which were not judged to be CGMP deviations, but could develop into deviations if uncorrected. The decision to take this approach was based on FDA’s experience that usually the formal response of foreign firms covered only FDA-483 items and not those only discussed orally. While this policy helps FDA elicit a more complete response from foreign firms, it does make it more difficult to compare CGMP compliance of foreign and domestic firms on the basis of FDA-483s.

Although used primarily for obtaining voluntary compliance, the FDA-483 does, admittedly, have a threatening side. If observations of significant CGMP deviations are ignored by a firm, then the FDA-483 along with the investigator’s oral discussion of these deviations with management can serve as the prior warning FDA usually needs to establish
before it can initiate severe regulatory actions such as a prosecution or an injunction.

**FDA-483 Related Problems**

**Exaggerated Importance of the FDA-483**

The Freedom of Information Act has no doubt helped to create a high level of both anxiety and interest in industry about the issuance and content of FDA-483s. For a firm receiving a FDA-483, publicity and possible misinterpretation can come quickly. For FDA watchdogs, the availability of FDA-483s issued throughout the country can provide valuable information about inspectional trends, the state of the industry, and FDA policy. But unless they are approached critically with an awareness of their limitations, they can mislead and send alarming false signals. And, in my opinion, they are particularly unreliable, if used alone to evaluate the CGMP compliance status of individual firms. For example, it would be foolish to automatically assume that a firm was in compliance with CGMPs just because the last investigator did not leave a FDA-483 or conversely that a firm was sadly out of compliance because several items appeared on one.

Certainly a factor in the extreme importance attached to the FDA-483 is the use of FDA-483 related elements in the performance plans for drug industry personnel. Some plans call for FDA-483 free inspections; others limit the number of permitted observations on the FDA-483. There are better “bottom line” measures of CGMP compliance as explained in the following paragraphs.

I believe that much of the exaggerated importance assigned to the FDA-483 comes from an incomplete understanding of the regulatory context in which it exists and the different levels of review it undergoes. Below I will attempt to provide some information about that context and the review process.

The FDA-483 does not exist in isolation. The investigator who issued the FDA-483 will also write a report, the establishment inspection report (EIR). The report will explain the significance of the listed observations and describe any corrections made during the inspection. (FDA policy does not permit the reporting of these corrections on the FDA-483.) The investigator will report discussions held with management during the inspection concerning CGMP deviations and planned corrections. Any management objections to the observations will also be reported. Before a district decides that a firm is not in compliance both the EIR and FDA-483 are critically reviewed by both the investigator’s supervisor and a compliance officer. (Some districts have recently reorganized around “teams” who carry out the critical review process.)

The district’s final compliance decision is recorded on two separate cover sheets to the EIR, the FDA-481(a) and the FDA-481(e). The FDA-481(e) is the written endorsement which discusses the inspectional findings and recommends the appropriate action to be taken. The FDA-481(a) is marked with the coded classification. Inspections requiring regulatory action are coded “A” while those requiring voluntary correction are coded “E”. “N” is used if no action is required. The “bottom line” of a district’s assessment of the compliance status of a firm is provided by the FDA-481(a) and (e); not the FDA-483.

The demands of the “A” classification may be met by the issuance of a warning letter. District directors may issue warning letters to dosage form manufacturers concerning CGMP deviations without review by headquarters. However, warning letters to bulk drug substance producers must be reviewed by the Center for Drug Evaluation and Research’s (CDER) Drug Manufacturing and Product Quality (HFD-320) unit before issuance. In all cases involving a severe regulatory action such as an injunction or prosecution this same unit reviews the EIR and the FDA-483 before a decision is reached. A long FDA-483 does not guarantee the approval of a recommendation for a regulatory action. As has happened in the past, the listed observations may simply be considered to be of little significance or to only reflect district or regional policy rather than national FDA policy.

**Variation in Inspectional Coverage Reflected on the FDA-483**

All investigators have heard the plaintive statements: “But the last investigator didn’t leave a FDA-483!” and “The last investigator thought everything was O.K.” These excuses carry little weight with FDA. Drug manufacturers have the primary responsibility for assuring that CGMP requirements are met. They cannot shift that responsibility to FDA investigators by only correcting conditions that appear on a FDA-483. However, the appeal of this convenient excuse seems hard to avoid. And it’s certainly not new to FDA judging from Commissioner Crawford’s testimony in 1953 about FDA’s experiment with written inspectional observations in the late 1920’s.

These differences in the assessment of the same operation among investigators usually are the result of differences in what they choose or are directed to cover during a particular inspection. What they choose to cover most commonly reflects their expertise and interests; their strengths and weaknesses. It’s only natural for an investigator to spend more time covering those things he or she knows most about or in which they have a special interest. My experience is that investigators show much more variation in what they choose to cover than they do in deciding what is or is not a CGMP deviation. Because of this variation in inspectional coverage among investigators, depending solely on the FDA-483 to gauge overall compliance with CGMPs is dangerous for the firm inspected and can be misleading to a third party.

**Length of FDA-483s**

Some FDA-483s have been misleading in their excessive length. This length can often be easily achieved by an exhaustive citation of each example of a system-wide problem. If this tactic is followed in reporting observations after a lengthy inspection, there is no real obstacle to producing a FDA-483 of 60 pages or more, except, of course, common sense. My impression has been that extremely long FDA-483s have often been produced as a kind of investigational tour de force, rather than simply as a means informing management of deviations that need to be
corrected. In short judging the CGMP compliance of a firm based on the length of a FDA-483 alone makes little sense.

FDA's policy covering the issuance of FDA-483s that was discussed earlier does not support overly long FDA-483s. It, in fact, cautions that "length is not necessarily synonymous with significance." But the temptation to use the number of pages of a FDA-483 as a kind of shorthand notation for the seriousness and extent of deviations found during an inspection has proven virtually irresistible within and outside FDA.

**Listing Items of Questionable Significance and/or Validity**

As we have seen, official FDA policy is not to list observations of questionable significance. However, at least some investigators in the past have not always followed that policy. They believed they needed to list a questionable condition "just to be safe." Also, there have been a few investigators who have listed questionable observations simply so they could issue a FDA-483 and demonstrate that they were doing their job. There are "human type" problems, hard to eliminate entirely. They once again show the need for caution and a critical approach in evaluating any FDA-483.

Firms sometimes accept observations of questionable validity and respond to them by making unneeded changes simply to avoid any possible delay in a NDA/ANDA approval or antagonizing the local FDA office. Sometimes this results in naming an unnecessary piece of new equipment or construction, usually in good humor, after the investigator. For trivial observations of no special consequence, this kind of unquestioning response is probably harmless. It is not so harmless in other situations. In fact, many in the drug industry feel strongly that by passively accommodating the sometimes extreme opinions of individual investigators, industry itself, unreasonably expands the boundaries of CGMP.

**Conclusions**

In 1953, the drug industry saw no need for congress to amend the FD&C Act to require FDA to issue a written report of insanitary conditions at the end of inspections. The FDA-483 owes its existence to the mid-western tomato canning industry; not the drug industry.

The Kefauver-Harris Drug Amendments of 1962 required that drug manufacturers follow current good manufacturing practices. However, it contained no requirement that FDA issue a written report of deviations from these practices. Such a requirement was contained in proposed legislation introduced in 1960. In other words, congress considered and rejected a requirement for FDA to issue a written list of CGMP deviations at the conclusion of drug inspections. FDA issues such written lists on the FDA-483 as a matter of policy to gain voluntary compliance: not because they are legally required to do so.

The FDA-483 is not a document that records FDA's evaluation of the GMP compliance status of any firm. Issuance of a FDA-483 does not necessarily mean that a drug firm is not in GMP compliance. Conversely, if an investigator does not issue one, it does not guarantee that a firm is in CGMP compliance. Its length is not a reliable indicator of the seriousness of the conditions observed by the investigator. Nor does it, with certainty, reflect FDA's GMP policy or shifts in that policy.

A FDA-483 should not be viewed uncritically by the receiving firm or third parties attempting to determine the compliance status of the firm or shifts in FDA policy. If a firm feels that it has received a FDA-483 containing questionable observations of GMP deviations, the items should be discussed thoroughly with the investigator. If unresolved, the issues should be discussed with the district director or regional director or CDER if necessary.

Finally, the use of FDA-483 elements in industry performance plans should be reconsidered. More reliable measures of CGMP compliance are available such as the final district classification of an inspection report.

**References**

An Authorized User of the electronic PDA Journal of Pharmaceutical Science and Technology (the PDA Journal) is a PDA Member in good standing. Authorized Users are permitted to do the following:

- Search and view the content of the PDA Journal
- Download a single article for the individual use of an Authorized User
- Assemble and distribute links that point to the PDA Journal
- Print individual articles from the PDA Journal for the individual use of an Authorized User
- Make a reasonable number of photocopies of a printed article for the individual use of an Authorized User or for the use by or distribution to other Authorized Users

Authorized Users are not permitted to do the following:

- Except as mentioned above, allow anyone other than an Authorized User to use or access the PDA Journal
- Display or otherwise make any information from the PDA Journal available to anyone other than an Authorized User
- Post articles from the PDA Journal on Web sites, either available on the Internet or an Intranet, or in any form of online publications
- Transmit electronically, via e-mail or any other file transfer protocols, any portion of the PDA Journal
- Create a searchable archive of any portion of the PDA Journal
- Use robots or intelligent agents to access, search and/or systematically download any portion of the PDA Journal
- Sell, re-sell, rent, lease, license, sublicense, assign or otherwise transfer the use of the PDA Journal or its content
- Use or copy the PDA Journal for document delivery, fee-for-service use, or bulk reproduction or distribution of materials in any form, or any substantially similar commercial purpose
- Alter, modify, repackaging or adapt any portion of the PDA Journal
- Make any edits or derivative works with respect to any portion of the PDA Journal including any text or graphics
- Delete or remove in any form or format, including on a printed article or photocopy, any copyright information or notice contained in the PDA Journal