FDA Form 483: Minimizing FDA Inspection Citations

One of the paramount issues related to FDA regulated products is that of documentation and record keeping related to manufacturing.

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FDA FORM 483

As an owner or manager of a company whose product is regulated by the FDA (Food and Drug Administration) you will, at some point, be subjected to an FDA inspection. And once an inspection is underway in your facility anything affecting the drug or food product directly or indirectly in an adverse manner is within the purview of the FDA inspectors.

If discrepancies are found during such an inspection, one or more Form 483 Inspectional Observation Forms will be submitted to company management addressing each discrepancy. These will come at the conclusion of the inspection process with each discrepancy being discussed and explained. Keeping in mind that the majority of discrepancies will typically be subjective in nature they can be wide-ranging in their impact and implication; from a housekeeping issue to product adulteration.

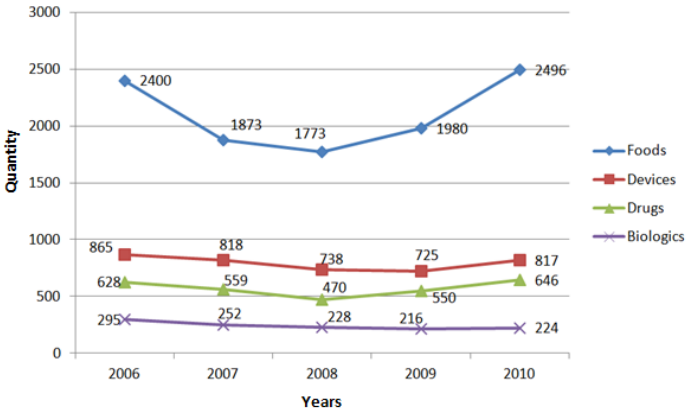

Chart 1 – 5 Years, 4 Categories, Number of 483's

The form 483 is a form used by the FDA as a first step in correcting a product related deficiency within a facility. Deficiencies can be related to computer programming, product contact material of construction, procedural issues, material handling, documentation, and on and on. Anything, as mentioned earlier, that could affect the consistent and acceptable quality of the product is fair game.

Rather than cover the broad and varied manufacturing Categories and subject matter encompassed by the use of Form 483 this discussion will focus more pointedly at those facilities that fall within the characterization of being included as a part of the Chemical Process Industry (CPI).

As a first step notification to facility management Form 483 is the FDA's way of identifying and forewarning a company that certain aspects of their manufacturing process are not compliant with FDA regulations. Upon receipt of a form 483 notification the company will have fifteen working days in which to respond. This is not a requirement, but is simply an expectation.

Should a company not respond within that fifteen day window, or should the response be considered insufficient or inadequate to correct the deficiency the second shoe would fall in the form of a Warning Letter being issued.

The Warning Letter would first state the issue or issues reiterating the Form 483 infraction(s), followed by a statement such as: "*We have reviewed your firm's response of December 12, 2012, and note that it lacks sufficient corrective actions*." The letter would then go on to elaborate, in significant detail, why the response was inadequate and what was required to rectify the issue.

In many cases the Warning Letter will include a cease and desist order, should its directive go unresolved or ignored, similar to what follows:

"*Until all corrections have been completed and FDA has confirmed corrections of the violations and your firm's compliance with CGMP, FDA may withhold approval of any new applications or supplements listing your firm as a drug product manufacturer. In addition, failure to correct these violations may result in FDA refusing admission of articles manufactured at ABC Drug Co., located at 1234 High Court, Gravesend, Kent, United Kingdom, into the United States*."

Note: The above company name and address is fictitious and is not intended to apply to any company in particular.

The letter will finish by giving the respondent "fifteen working days" to respond with a clear and concise description as to what steps have been taken or are to be undertaken to correct the listed deficiencies. Should those fifteen working days be exceeded with no effort at a response from the notified company then any penalizing action described in the Warning Letter will go into effect.

Published in March 2014 issue of Chemical Engineering magazine

Referring to Table 1, in a five year period from 2006 through 2010 there were a total of 78,242 FDA inspections encompassing eleven manufacturing Categories. These inspections resulted in 27,241 Form 483's being recorded. Chart 1 represents a portion of those statistics with four of the higher ranking manufacturing Categories providing a comparison between the four being represented. As readily seen, the food processing Category far and away seems prone to attract the most FDA citations.

FORM 483 STATISTICS

TABLE 1
FDA Inspectional Observations – Number of 483's Issued by Year

483 Totals	Year				
	2010	2009	2008	2007	2006
Sum Product Area 483s from System[1]	5306	4612	4307	4630	5383
Actual Total of 483s in System[2]	4804	4122	3805	4079	4747
Total 483s for Fiscal Year[3]	6695	5449	4764	4826	5507
Total Number of Inspections/Year	17635	15170	14318	14594	16525

NOTES:
1. This table does not represent the complete set of 483s issued during the fiscal year as some 483s were manually prepared and not available in this format. The sum of 483s for all Product Areas will be greater than the actual Total 483s issued during the fiscal year since a 483 may include citations related to multiple product areas, and counted more than once, under each relevant product center.
2. This is the Actual Total number of 483s issued from this system, and that are represented in this Table.
3. This is the count of the total number of 483s issued in and out of the system during a 1 year period.

FDA inspection and enforcement falls under the responsibility of the FDA's Office of Regulatory Affairs (ORA). While the majority of Form 483's are generated through the electronic TurboEIR (Turbo Establishment Inspection Report) form reporting system, which is reflected in the data used for Table 1 and Chart 1, there are some instances in which these forms are filled out manually and are therefore not represented in these statistics. TurboEIR generated 483's are categorized in the following manner:

- Biologics
- Drugs
- Devices
- Human Tissue for Transplantation
- Radiological Health
- Parts 1240 & 1250
- Foods (includes dietary supplements)
- Veterinary Medicine
- Bioresearch Monitoring
- Incidental Text
- Special Requirements

From October 1, 2009 through September 30, 2010 Table 2 reflects, by Category, the number of Form 483's issued from the TurboEIR system in descending quantity by category:

TABLE 2 – Form 483's Issued 10/1/2009 Thru 9/30/2010	
Category	Quantity Issued
Foods	2496
Devices	817
Drugs	646
Incidental Text	303
Bioresearch Monitoring	282
Veterinary Medicine	232
Biologics	224
Parts 1240 & 1250	169
Human Tissue for Transplantation	111
Radiological Health	16
Special Requirements	10
Total No. of 483's	5306
Total No. of Inspections Same Period	17635
% Inspection Having 483's	30%

INTERPRETING FDA REGULATIONS

The FDA inspectors, working through the ORA, are guided by three resources: The regulations set forth under Title 21 of the Code of Federal Regulations (CFR); Its law enforcement counterpart Title 21 Chapter IX of the US Code (USC); and their FDA training guidelines.

Training for FDA inspectors plays a big role in how they perceive, not only the rule of law under the USC, which by necessity is writ black and white, but to also understand the nuances and implications of the unwritten variants within the many complex guidelines and laws the manufacturer is obliged to follow under CFR Title 21 .

One of the difficulties lies in the fact that many regulations governing the manufacture of food, drugs, and cosmetics is, in many cases, intentionally vague. This is due in large measure to two basic facts:

1. Much of manufacturing is proprietary and specialized. It would be impossible to write detailed requirements that would apply to all manufacturing without constraining or interfering with development and inhibiting new concepts.
2. The criteria that the inspector must base their field analysis on is relative by nature and is subject to a sub-set of nuances that would be impossible to capture in words, making broad statements in the CFR a necessity.

This is why, in Title 21Chapter I Subchapter C Part 211 Subpart D, you will find such vague requirements as in Section 211.63, which states:

Published in March 2014 issue of Chemical Engineering magazine

- ***211.63 Equipment design, size, and location.*** *Equipment used in the manufacture, processing, packing, or holding of a drug product shall be of appropriate design, adequate size, and suitably located to facilitate operations for its intended use and for its cleaning and maintenance.*

The FDA cannot regulate the design of equipment, the size of equipment, or its location within a facility or its approximation to other equipment.

Or in Section 211.67 where it states, in part:

- ***211.67 Equipment cleaning and maintenance.*** *Equipment and utensils shall be cleaned, maintained, and, as appropriate for the nature of the drug, sanitized and/or sterilized at appropriate intervals to prevent malfunctions or contamination that would alter the safety, identity, strength, quality, or purity of the drug product beyond the official or other established requirements.*

In stating such a vague requirement it is leaving the design and procedural elements to industry. Without knowing a particular process the FDA cannot possibly know the specific needs of its cleaning requirements. What is available for the engineer or manufacturer instead is two sources to help meet FDA compliance. But before touching on these two very important sources let us take a look at what is currently happening in this industry.

In referring back to Table 2 you can readily see that with 2496 Form 483's issued in 2009 the "Foods" Category has, by far, the greatest number written against it; three times that of the second runner-up, Devices with 817 infractions. Of that 2496 an outstanding 61% were related to sanitary issues.

These sanitary issues include such incidents as rodent and insect infestations, improper or infrequent cleaning of equipment, and other sanitary issues having to do with waste, product storage, facility design, etc. This is an example of subjective calls made by the inspector regarding conditions that cannot be defined in simple black and white terms.

Such conditions are assessed based in large part upon what is contained in the broad set of parameters described in very general terms in Title 21 Chapter I Subchapter B Part 110 Subpart A Section 110.5 in which it states, in part:

- ***110.5 Current good manufacturing practice.*** *The criteria and definitions in this part shall apply in determining whether a food is adulterated (1) within the meaning of section 402(a)(3) of the act in that the food has been manufactured under such conditions that it is unfit for food; or (2) within the meaning of section 402(a)(4) of the act in that the food has been prepared, packed, or held under insanitary conditions whereby it may have become contaminated with filth, or whereby it may have been rendered injurious to health…*

What occurs in many cases, whether it's food or drug products, is that the manufacturer or engineer interprets the finer points of an industry law or regulation in one way while the inspector interprets it in another.

Case-in-point:

- An issue cited 51 times during the fiscal year 10/1/2009 to 9/30/2010 concerned equipment used in the manufacture, processing, packing or holding of drug products that was not of appropriate design, of adequate size, or suitably located to facilitate operations for its intended use, cleaning, or maintenance.

- In that same time period there were 61 cited incidents in which equipment and utensils were not cleaned, maintained, and sanitized in an appropriate manner or at appropriate intervals to prevent malfunctions and contamination that could alter the safety, identity, strength, quality or purity of the drug product.

- In addition to the two different types of incidents above there were many other incidents that are too numerous to mention here, but one other does stand out…significantly. Over the same time period mentioned above there were in excess of 1000 cited incidents concerning documentation in which:

    - Written procedures were non-existent,
    - Written procedures were not followed,
    - No written record of investigations,
    - No cleaning & maintenance records,
    - No periodic review of procedures,
    - No written sanitation procedures,
    - And others related to documentation.

DOCUMENTATION

One of the paramount issues related to FDA regulated products, again, whether it's food or drug products, is that of documentation and record keeping related to manufacturing. These industries repeatedly get hammered on this same issue. It begins with documentation required to cover traceability of the product contact material used in constructing process systems and run the gamut to include properly written process descriptions and cleaning

procedures to weld logs and material certification documents.

If metallic material, such as tubing or equipment, is used for product contact material it will require traceability in the form of a heat number that can be traced back to the mill of origin. The heat number is the tracking number found on the Mill or Material Test Report (MTR). If it is non-metallic it will require a Certificate of Compliance (C of C) for batch traceability back to its source of formulation.

This is all done with the intent to hold originating and modifying parties of a raw or finished product accountable should such a product be determined the source cause for adulterating a food, drug, or cosmetic product during production or post production handling.

The material used to build the systems that manufacture food, drugs, and cosmetics have been carefully selected and enhanced over the years to prevent contamination of a product through the inadvertent introduction of undesirable particulates into the product stream. This can occur through the leaching of non-metallic material or the use of poorly passivated stainless steel that could introduce iron oxides into the product stream.

Procedures should be written and followed, not only for the process itself, but for Clean-In-Place (CIP) and Steam/Sanitize-In-Place (SIP) procedures as well. All maintenance and quality control procedures should be written and followed, with signed and dated log reports verifying the frequency and intervals in which these activities were performed.

Well written procedures, records, and documentation are not only proof to the FDA inspectors that well thought-out operational programs were put in place, but it shows due diligence on behalf of the company that management takes seriously the safe and controlled manufacture of food, drugs, and cosmetics.

The ease of access to appropriate documentation, its thoroughness, and organization will pay dividends, not only for the FDA inspection process, but also for the company's bottom line with regard to well controlled manufacturing and processing.

REGULATORY BLIND SPOTS

Getting back to the two sources for resolving the issue of filling in the blanks left by the vague regulatory requirements in Title 21 Chapter I Subchapter B Parts 110 & 111(for food) and Subchapter C Parts 210 & 211 (for drugs). Following is an appropriate and rather easy way of helping to resolve this issue.

As mentioned earlier, with regard to the FDA inspectors being trained to understand the nuances and implications of the unwritten variants in the FDA regulations, the best way to see what they see and to understand their expectations is by studying their training documents.

There are a set of "Inspection Guides" and "Inspection Technical Guides" used in the FDA inspector's training that are available at no cost and can be found at http://www.fda.gov/ICECI/Inspections. At this site you will also find access to other guides used by FDA inspectors such as:

- Field Management Directives
- IOM: Investigations Operations Manual
- Guide to International Inspections and Travel
- Medical Device GMP Reference Information
- QS Regulation/Design Controls

There are also reams of Guidance documents that can be found for drug related regulations at (http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm) and for food related regulations at (http://www.fda.gov/Food/GuidanceComplianceRegulatoryInformation/default.htm). Much of the information found at these sites are simply regurgitated from what is written in the related CFR documents. It is provided in a somewhat easier to read format.

Reading the training and guidance literature and learning what it is the inspectors are trained to look for in specific cases will put your engineering, operations, and manufacturing personnel on the same page with what the inspector's expectations will be when they set foot inside your facility.

To go further in finding guidance when having to comply with regulatory requirements, as it relates to the Chemical Process Industry (CPI) and the FDA, specific organizations such as 3-A Sanitary Standards, Inc. (3-A SSI), ISPE (International Society of Pharmaceutical Engineers), and ASME-BPE (American Society of Mechanical Engineers – Bioprocessing Equipment) standards, provide a great deal of specific insight, guidance, and answers that help fill the void not expressed or defined in the regulations themselves.

Looking to such resources as the FDA training literature mentioned above and qualified industry standards, also mentioned above, will help any engineer or manufacturer through the mine field of regulatory compliance and help build a better facility in the process.

INDUSTRY STANDARDS

In referring back to the previously mentioned requirements stated in Title 21Chapter I Subchapter C Part 211 Subpart D Section 211.63, such vague regulatory requirements are looked at, assessed, studied, defined, and vetted by the membership of accredited American National Standards Developers; the final results of which is published for industry use. These assessments and studies are done by industry experts that invest themselves in the committees that make up the various industry-related standards organizations.

In this particular case, regarding Section 211.63, you can turn to the ASME-BPE Standard Part SD to find specific detailed information that will assist the engineer in meeting the essential requirements of Section 211.63 when it states, "*…appropriate design, adequate size, and suitably located to facilitate operations for its intended use and for its cleaning and maintenance*."

ASME-BPE Part SD explains in graphic detail what designs are acceptable with regard to vessels, pump seals, nozzle attachments, etc.

Or, in the case of the earlier mentioned Title 21Chapter I Subchapter C Part 211 Subpart D Section 211.67 "Equipment Cleaning and Maintenance", more specific details can be found in the ASME-BPE Standard on clean-in-place and steam (sanitize)-in-place system requirements.

ISPE offers regulatory compliant guidelines on water and steam system design; system maintenance; final treatment technologies and basic system configurations related to the generation process of compendial purified water, highly purified water, non-compendial waters, and much more.

3-A SSI provides detailed guidance on the processing, handling, and transport of food, dairy, and beverage products, with a relatively new standards committee for Active Pharmaceutical Ingredients (API) equipment. This group is referred to as P3-A.

FDA INSPECTION GUIDELINES

With types of water being a common denominator between the various FDA regulated industries we can use it as an example of how the FDA Inspection guides can be utilized by the engineer. For this we will refer to the FDA's "Guide to Inspections of High Purity Water Systems", which can be found at:

http://www.fda.gov/ICECI/Inspections/InspectionGuides/ucm074905.htm

This guide touches on:

I. System Design
II. System Validation
III. Microbial Limits
IV. Water For Injection Systems
V. Still
VI. Heat Exchangers
VII. Holding Tank
VIII. Pumps
IX. Piping
X. Reverse Osmosis
XI. Purified Water Systems
XII. Process Water (numbered as XIII on web site)
XIII. Inspection Strategy (numbered as XIV on web site)

As an example of what can be used as take-aways from an Inspection Guideline is represented in the following paragraph pulled from Paragraph II "System Validation". In it, the third paragraph states:

"*In the review of a validation report, or in the validation of a high purity water system, there are several aspects that should be considered. Documentation should include a description of the system along with a print. The drawing needs to show all equipment in the system from the water feed to points of use. It should also show all sampling points and their designations. If a system has no print, it is usually considered an objectionable condition. The thinking is if there is no print, then how can the system be validated? How can a quality control manager or microbiologist know where to sample? In those facilities observed without updated prints, serious problems were identified in these systems. The print should be compared to the actual system annually to insure its accuracy, to detect unreported changes and confirm reported changes to the system.*"

There are seven key take-aways from the "System Validation" paragraph that includes the need for:

1. Preparation of a validation report,
2. written description of the piping system,
3. a representative isometric drawing of the system,
4. drawings that show all equipment,
5. drawings that show identified sampling points,
6. point of use locations (with identifiers), and
7. a quality management system that should include a process by which there is a requirement to walk down each system on a periodic basis at intervals that do not exceed a twelve month period in order to verify the system's as-installed condition.

CONCLUSION

While there is so much more to be said with regard to the FDA's Form 483, and the Warning Letter for that matter, an essential point is that the FDA inspection process should not be treated like a thorn in the side. It should instead be treated as if you were working with a third-party inspector, an inspector with a little more force behind their decisions.

The key factor in all this is arguably the rules of engagement. As long as an owner or engineer understands the rules that the FDA inspector is playing by an acceptable inspection result (read low 483 count) is certainly attainable. An acceptable inspection result is considered here to be one in which the inspection report would result in zero 483's or even one with a few minor 483's.

The basic disconnect lies in what the FDA inspector expects to see and how the owner/engineer plans to meet that expectation. In order to meet at that crossroads the owner or engineer should preemptively develop a set of design and engineering specifications based on what can be gleaned from the three sources mentioned throughout this discussion. This would include, as represented in Chart 2: Proper CFR's, FDA Inspector Training Guides, and Industry Standards.

Looking at the FDA inspector as a third-party inspector, rather than the black arm of the Gestapo, will help a company understand them more as a beneficial asset and less as a hindrance. Unless a company is subversively attempting to circumvent regulations by skipping steps in the regulatory process, or is simply trying to keep cost down at the risk of food or drug adulteration then an audit, however painful it might seem at the outset, should be looked upon as an incremental, beneficial, and integral part of the design, engineering, construction, and commissioning process.

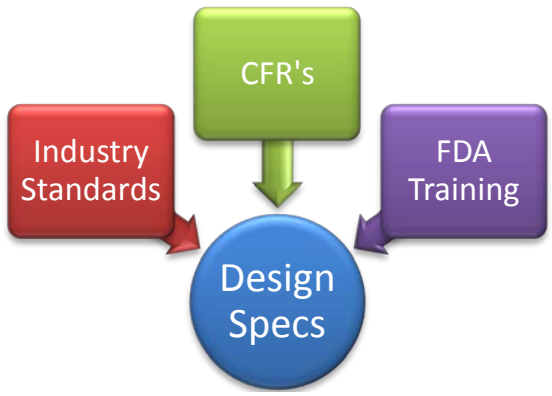

Chart 2 – Developing Design Specifications

From a very fundamental perspective all of us should be designing and building facilities that manufacture product intended for human consumption and cosmetic application in a manner that will produce a product that is inherently safe in a consistent and verifiable manner with an overreaching consideration toward public health. The job of the FDA inspector is to verify that we are doing just that.

Bibliography:

ASME-BPE Standard
(http://www.asme.org/groups-(1)/technical-institutes-and-divisions/bioprocessing-equipment)

ISPE (International Society of Pharmaceutical Engineers)
(http://www.ispe.org/)

3-A SSI (3-A Sanitary Standards, Inc.)
(http://www.3-a.org/)

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Published in March 2014 issue of Chemical Engineering magazine