Five Tips on Writing an Effective 483 Response

Background

FDA inspections of human cell tissue and tissue-based products (HCT/Ps) facilities are on the rise, as are the number of inspections which result in either those resulting in either a voluntary action indicated (VAI) or an official action indicated (OAI). An FDA report[i] summarizing HCT/P inspections performed in fiscal years 2003 to 2012 shows that the number of inspections performed has jumped from 227 in 2003 to 592 in 2012. As the number of inspections has increased, so has the number of VAIs and OAIs—in 2003, 33.1% inspections resulted in a VAI; in 2012, 34.95% did. Similarly, 3.13% of all inspections in 2003 resulted in an OAI; in 2012, 3.47% did.[ii] (See FDA charts in Appendix A.)

Under the Federal Food, Drug, and Cosmetic Act, SEC. 704 (21 USC §374), FDA is authorized to perform inspections and such inspections can result in a Form FDA 483, is a form used by the FDA to document and communicate concerns – or "inspectional observations" – discovered during these inspections. Commonly referred to as "Form 483" or just "a 483" it includes this preprinted instruction: **''This document lists observations made by the FDA representative(s) during the inspection of your facility. They are inspectional observations; and do not represent a final agency determination regarding your compliance. If you have an objection regarding an observation, or have implemented, or plan to implement corrective action in response to an observation, you may discuss the objection or action with the FDA representative(s) during the inspection or submit this information to FDA.''**

The 483 was born as a result of the Factory Amendments of 1953 to the Federal Food, Drug and Cosmetic Act[iii]. Prior to that time, FDA inspection results were not reported to management at the conclusion of an inspection. The inspection authority contained a "Catch-22" in that FDA had to obtain "permission of the owner, operator or agent in charge" before beginning an inspection, but the withholding of that permission was a criminal act…so, in essence, the concept of "permission" was misguided. In *United States v. Cardiff*, (344 U.S. 174)[iv], the court held that the Food, Drug and Cosmetic (FD&C) Act did not mandate that consent be given to warrantless inspections of establishments covered by the Act. As a result, the statute was subsequently amended to read as it does today, and the requirement for FDA to provide a report to management at the end of the inspection was added to the law. The observations are just that—observations; they do not represent a final FDA determination regarding compliance.

When is an FDA Form 483 issued?

According to the FDA, "An FDA Form 483 is issued to firm management at the conclusion of an inspection when an investigator(s) has observed any conditions that in their judgment may constitute violations of the FD&C Act and related Acts. FDA investigators are trained to ensure that each

observation noted on the FDA Form 483 is clear, specific and significant. **Observations are made when in the investigator's judgment, conditions or practices observed would indicate that any food, drug, device or cosmetic has been adulterated or is being prepared, packed, or held under conditions whereby it may become adulterated or rendered injurious to health.**"[v]

The FDA Form 483 is just an initial report; it does not constitute a final Agency determination of whether any condition is in violation of the FD&C Act. Before making the decision whether or not to issue a warning letter, the FDA considers the 483, along with a written report called an Establishment Inspection Report (EIR), all evidence or documentation collected on-site, and any responses made by the firm. If FDA determines, based on all this documentation, that the firm is in violation of the FD&C Act or another statute that they enforce, they may issue a warning letter. Warning letters are issued only for significant violations that may lead to enforcement action if they are not immediately and adequately corrected.

What is required after receiving a 483?

The law does not require that you respond to a 483 at all; however, "companies are encouraged to respond to the FDA Form 483 in writing with their corrective action plan and then implement that corrective action plan expeditiously." Response must be swift – within 15 business days of the issuance of the form.

In the *Federal Register* of August 11, 2009[vi], FDA posted a new policy regarding timeliness of the written response to a 483. In that policy, FDA states that delayed and multiple responses to a 483 have resulted in delays in issuance of warning letters and, to that end, they are establishing a program to establish a timeframe for the submission of such post-inspection responses to the 483 for FDA's consideration in deciding whether to issue a warning letter. Under the program, the agency will not delay the issuance of a warning letter in order to review a response to a 483 that is received more than 15 business days after the form was issued. If FDA does go on to issue a warning letter after reviewing a firm's response within that 15 business day window, the warning letter will recognize receipt of the response and will incorporate the response into the warning letter's recommendations. If FDA receives a response to the observations more than 15 business days after the 483 was issued, they will not address the adequacy of the firm's reported corrective actions. **The bottom line is that if you want your response to the 483 to be considered by the FDA as part of their decision to issue a warning letter, you must get your written response to the agency within 15 business days.**

Tips on Responding to a 483

1. **Respond in writing within 15 days.** While there is no regulatory requirement to respond to the 483, it's in your best interest to respond in writing. A well-reasoned, complete 483 response could possibly mitigate an FDA compliance decision for further action. Submitting this response in a timely manner demonstrates to FDA and other stakeholders that the facility is aware of the FDA's concerns and understands the observations and demonstrates a commitment to voluntarily comply with the recommendations. Furthermore, submitting the response in writing

establishes credibility with FDA. It is imperative that you respond to the 483 within 15 days; otherwise, FDA may not consider your response at all and may proceed with issuing a warning letter.

2. **Include a statement from senior leadership.** Providing a statement from senior leadership demonstrates to FDA that the facility understands the importance of the observations and is committed to addressing each in a thorough manner. It also offers an opportunity to express whether senior leadership agrees or disagrees with the observations.
3. **Provide corrective action accomplished and/or planned.** Be specific and complete, addressing each observation individually. Format your response to address each observation noted in the 483 individually. List the actions you plan to take to address the observation, why you believe the proposed action will be sufficient to address the concern, the date by which you plan to complete the action(s) and the steps you intend to take to ensure the corrective action(s) had the intended effect. Address affected products and provide realistic measures for improvement, as you will want to be sure to be able to deliver what you promise within the timeframe you specify.
4. **Provide method of verification and/or monitoring for corrections.** For each observation you respond to, be sure to state why you believe the observation occurred. Thoroughly and adequately express what you believe to be the root cause of the observation, as well as how the observation would potentially impact product quality and safety. Specify what you believe to be the scope of impact and how you determined such scope. Spell out the intended corrective actions and how the improvement will be measured—e.g. audit or monitoring. Include any relevant records of inspection, calibration or other quality assurances.
5. **Provide time frames for correction.** In addition to detailing **what** action you plan to take for each observation noted in the 483, it is important that you also indicate **when** you plan to complete the action. Indicate date by which correction or review will be completed and assure that documentation of the correction will be submitted to FDA upon completion. If the observation requires ongoing monitoring or assessment, set target dates for ongoing actions and according documentation submission to FDA. Key to this step is establishing an effective quality system that includes proper documentation, implementation and ongoing measurement.

How AABB Consulting Services Can Help

Responding to a 483 is just the first step of what can be an arduous journey to establishing appropriate processes and systems to ensure compliance with FDA regulations and avoid future regulatory actions. This is where AABB Consulting Services can help. For over a decade, AABB Consulting Services has provided expertise in quality management and process improvement in the fields of transfusion medicine, cellular therapies and blood management. We have helped hundreds of facilities address issues such as those outlined in 483s and overcome potential violations. Our vast experience in helping facilities build a foundation of excellence in quality and compliance allows us to hit the ground running – swiftly and effectively responding with a defined corrective action plan and the ability to implement the plan without upsetting your operations and staffing. So when you're faced with a regulatory challenge,

whether it's responding to a 483 or an OAI, contact AABB Consulting Services and let us help you respond and move forward with confidence.

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[i] HCT/P Inspection Information http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ComplianceActivities/ucm136342.htm

[ii] Average Time FDA Takes to Conduct HCT/P Facility Inspections on the Rise http://www.raps.org/focus-online/news/news-article-view/article/2822/average-time-fda-takes-to-conduct-hctp-facility-inspections-on-the-rise.aspx

[iii] FDA Inspection Observations - The FDA-483 and Beyond http://www.ispeboston.org/files/fda_483_chesney.pdf

[iv] 344 U.S. 174 (1952) United States v. Cardiff. http://scholar.google.com/scholar_case?case=12105327826055786068&hl=en&as_sdt=2&as_vis=1&oi=scholarr

[v] FDA Form 483 Frequently Asked Questions http://www.fda.gov/ICECI/EnforcementActions/ucm256377.htm

[vi] Federal Register/ Vol. 74, No. 153 / Tuesday, August 11, 2009 / Notices http://www.gpo.gov/fdsys/pkg/FR-2009-08-11/pdf/E9-19107.pdf

About AABB Consulting Services

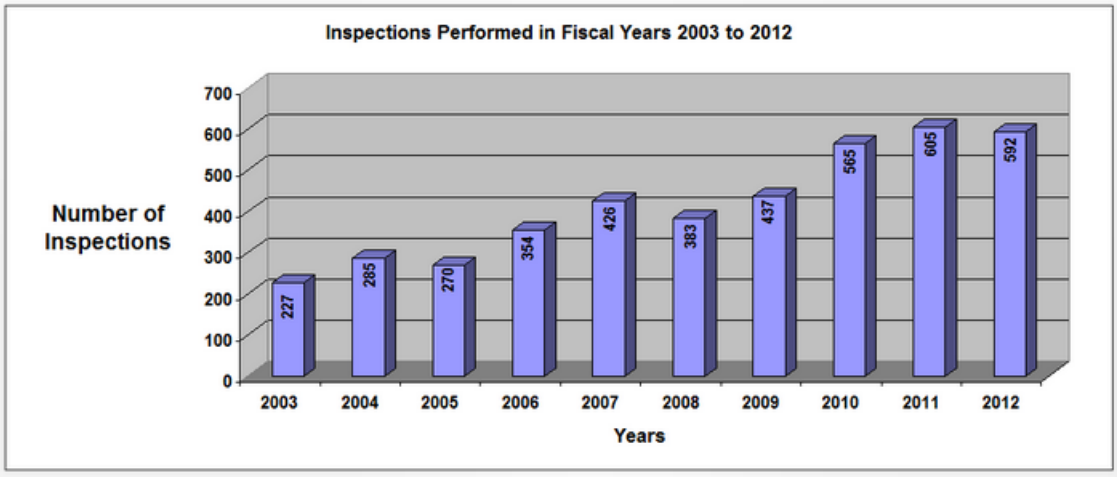
For over a decade, AABB Consulting Services has provided expertise in quality management and process improvement in the fields of transfusion medicine, cellular therapies and blood management. Faced with an increasingly complex landscape—from rapidly evolving research and product development to growing regulation—facilities worldwide have turned to AABB Consulting Services to relieve the burden of evaluating and developing quality systems, SOPs and compliance so you can focus on your core business. Whatever your challenge, AABB has been there and done that. Our consultants possess the highest level of expertise, professionalism and technical knowledge and we keep these core values in the forefront to guide our business practices.

Ready to get started, or want to chat to see if AABB Consulting Services can help? Contact us today.

Appendix A

HCT/P Inspection Information

Inspections Performed in Fiscal Years 2003 to 2012



Inspection Conclusion by Fiscal Year

	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
Inspections Classified NAI *	160	233	217	249	308	285	309	414	494	432
Inspections Classified VAI	53	43	46	96	113	90	112	135	110	151
Inspections Classified OAI	5	7	0	10	9	11	14	12	13	15
Avg. hours per Inspection	33.1	33.7	32.2	44.7	46.7	37.5	41.7	41.7	39.9	39.4

***NAI** = No Action Indicated, meaning no objectionable conditions or practices were found during the inspection (or the significance of the documented objectionable conditions found does not justify further action).

VAI = Voluntary Action Indicated, meaning objectionable conditions were found and documented but the agency is not prepared to take or recommend regulatory action.

OAI = Official Action Indicated, meaning objectionable conditions were found and regulatory action should be recommended.

(See also the "ORA Field Management Directive No. 86, Establishment Inspection Report (EIR) - Inspection Conclusions and District Decisions, June 7, 2007" in the Related Information box on this page.)

[1] Sum of inspection classifications does not equal total number of inspections performed by fiscal year due to data constraints

(Source: U.S. Food and Drug Administration website)