

Tips for Effectively Responding to a Form FDA-483 for Foreign Medical Device Manufacturers

Provide a detailed response plan, thorough documentation and translations.

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The manufacture of medical devices abroad for import into the United States presents regulatory risks and challenges for foreign device manufacturers and their U.S. importers. The U.S. Food, Drug, and Cosmetic Act (FDCA) authorizes the U.S. Food and Drug Administration (FDA) to refuse admission of medical devices to the United States that “appear” to be adulterated or misbranded. As a result, an FDA inspection that finds significant deficiencies in a foreign manufacturer’s quality system can interrupt the importation of medical devices into the United States.

Although FDA inspects approximately 5 percent of foreign Class II and Class III medical device establishments each year, as compared to 27 percent of domestic facilities,¹ the chances that a foreign inspection will result in a warning letter are higher than that for a U.S. manufacturer. Approximately 40 percent of warning letters issued to foreign manufacturers include notice of conditions that support detention without physical examination, otherwise known as automatic detention. A foreign manufacturer that is under an automatic detention order (or its shipper or importer) must prove to FDA that its products are not adulterated before those products can be released by U.S. Customs.² This has the effect of delaying or restricting the importation of the devices into the United States.

The higher rate and severity of warning letters issued to foreign manufacturers may be explained, in part, by the fact that the FDCA imposes a higher standard for devices that are imported into the United States than for those manufactured domestically. Section 801(a) of the FDCA³ requires FDA to refuse admission of a device into the United States if it “appears” that the device is adulterated or misbranded.⁴ By comparison, the FDCA prohibits the introduction or delivery in interstate commerce of a domestically manufactured

device that is adulterated or misbranded. As a result of this difference in the statutory standard, FDA investigators are permitted to collect less documentary evidence to establish violations by foreign device manufacturers.⁵ It is therefore important for foreign device manufacturers to take steps following an FDA inspection to promptly and effectively address any deficiencies identified by the FDA investigator.

At the close of an inspection, the FDA investigator typically will issue a Form FDA-483, “Inspectional Observations.” The FDA-483 contains a list of deficiencies in the manufacturer’s quality system, as well as deviations from other regulatory requirements. Companies have the opportunity to respond to the observations presented in the FDA-483 following the close of the inspection. Based on the investigator’s observations and the company’s response to the FDA-483, FDA will decide whether to issue a warning letter.⁶ An effective response to the FDA-483 can be an important consideration in FDA’s determination of whether to issue a warning letter and whether an automatic detention is warranted.

Preparing an effective response to an FDA-483 can be difficult, particularly for foreign manufacturers who may be inspected infrequently and unfamiliar with FDA’s inspection and enforcement processes and procedures. FDA discussed the responses the agency had received to the FDA-483 in 150 of the 238 warning letters issued to foreign medical device manufacturers posted in “FDA’s Electronic Freedom of Information Reading Room—Warning Letters and Responses.” FDA determined that only nine of the 150 responses adequately addressed the issues identified in FDA-483. FDA’s discussion of the companies’ responses in the warning letters provides insights into common deficiencies in those responses and suggests important lessons that may en-

able foreign companies to more adequately and effectively respond to FDA’s concerns. The following eight lessons are drawn from a review of foreign warning letters issued between 2003 and 2007, which discuss manufacturers’ responses.

Lessons for Responding to Forms FDA-483

1. Understand the issues cited in the FDA-483, and respond directly to them.

As a threshold matter, foreign medical device manufacturers may benefit from soliciting regulatory and technical advice to ensure the company understands precisely the deficiencies FDA cited in the FDA-483 so any corrective action the company takes is directly and fully responsive to FDA’s concerns. Foreign medical device manufacturers that have limited experience dealing with FDA frequently find they are communicating with the agency at cross-purposes. For example, in a warning letter issued on April 24, 2007, to a United Kingdom firm, FDA cited the company for failing to validate a process involving automated machinery.⁷ The firm’s response to FDA-483, however, provided information regarding the qualifications of its automated machinery and did not address validation of the process that employed the machinery.⁸ In the warning letter, FDA stated that the firm “confused process validation with equipment qualification.”⁹

2. Response plans should go beyond simply correcting the observations by also addressing the underlying risks and concerns.

Two critical factors in addressing any FDA observation are to determine if the appropriate actions have been taken to address the deficiency and to mitigate any resulting risk to that or related products or processes. In reviewing a company’s response to FDA-483, FDA will consider whether the change or changes should have extended beyond the action taken to address the specific problem. When further action is deemed unwarranted, manufacturers should include an explanation as to why the actions taken are sufficient to ensure product quality.

For example, in a warning letter issued to a Taiwanese firm, FDA concluded that the manufacturer’s response to the FDA-483 was inadequate “because the firm’s product modification procedure... does not

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require validation of the change or provide criteria when verification alone is appropriate. The firm did not provide justification for not performing validation.”¹⁰ The firm’s response left FDA unable to determine whether the corrective actions taken were adequate to address the underlying concern and whether further actions were unnecessary. Providing either a detailed explanation of the adequacy of the corrective action or conducting a more fulsome action plan may have avoided the need for FDA to issue a warning letter on this issue.

Similarly, in a warning letter issued on July 17, 2007, FDA cited a Canadian firm for “using [an] unapproved procedure... for verification of product labeling,” noting that during the inspection, the firm was in the process of approving the procedure.¹¹ FDA concluded that simply approving the procedure was insufficient because “there was no evaluation made for corrective and preventive actions. Signing off on the corrected SOP [standard operating procedure] version does not resolve the issue; it is merely a correction.”¹² This highlights the importance of considering what other actions may be appropriate to address observations in an FDA-483, beyond the correction to the specific observation, and explaining, in the response, the rationale for

taking or not taking such further actions.

FDA’s Regulatory Procedures Manual further highlights the need for comprehensive and rigorous corrective action.¹³ The manual states that, in considering whether to issue a warning letter, FDA evaluates “the overall adequacy of the firm’s corrective action and whether the corrective action addresses the specific violations, related violations, related products or facilities, and contains provisions for monitoring and review to ensure effectiveness and prevent recurrence.”¹⁴ FDA’s Quality System Inspection Technique (QSIT) provides specific guidance on how FDA conducts system audits and describes the actions to consider when implementing “a product or process change to correct a reliability problem or to bring the product into conformance with product specifications.”¹⁵ According to FDA’s QSIT guide, specific actions to consider when reviewing the adequacy of a product or process change include “changes in component supplier, training, changes to acceptance activities, field action [i.e., recall] or other applicable actions.”¹⁶ With any type of deficiency, manufacturers should consider how the deficiency ultimately affects product quality and what other actions are appropriate to address the deficiency.

3. Procedures included in a response should provide a greater level of detail than would otherwise be necessary.

In developing new procedures in response to observations in an FDA-483, it is important to understand the purpose of the underlying regulation being cited by FDA. It is essential to consult the appropriate regulations and guidance such as FDA’s QSIT guide.¹⁷ It also is important to consult with legal and technical experts to ensure FDA’s regulations and guidance are interpreted and implemented appropriately. The new procedure should cover each element of the applicable regulation, with a level of detail that suggests the procedure is not merely parroting the language of the regulation. The more concrete the details in the procedure (as opposed to providing only an abstract overview), the more valid the procedure will appear to FDA.

Firms should describe new and modified procedures in sufficient detail to permit FDA to confirm the adequacy of both the procedure and its implementation. For

example, FDA noted in a warning letter issued on January 16, 2007, that a Belgian firm's "revised procedure [contained in the firm's response] makes reference to 'statistic data'... This response is... inadequate because the procedures must define what statistical methods will be used, when they will be used, and how that information is to be utilized with respect to the requirements in [the firm's system]."¹⁸ Similarly, in a warning letter issued on April 7, 2003, FDA stated that the design control procedure submitted by a Canadian firm was only "an outline of requirements... there is no instruction as to how to actually implement the procedure."¹⁹

While smaller companies can usually employ less-detailed processes, procedures written in response to an FDA-483 following a foreign inspection should include "the detail necessary to define what is to be done, who is responsible and how it is to be completed."²⁰ This detail will allow FDA to confirm that the procedure will appropriately address the issues noted, without having to review the procedure in action.

4. When investigating an observation, look beyond batch records and other immediate sources of data to identify the problem.

FDA will not consider an investigation complete unless the firm conducts a review as thorough as that which an FDA investigator would conduct during an inspection. For example, in a warning letter issued on May 26, 2006, to a German firm, FDA determined that the company's conclusion as to the cause of a reported complaint was inadequate based on the company's investigation.²¹ FDA noted that the firm was "unable to identify any deviations in the batch documentation as it pertained to in-process and final controls."²² FDA noted that even though the firm "reviewed records related to the deviation, there is no documentation to show [that the firm] evaluated the process, or if an assessment [was] made to determine if the information routinely recorded on the batch records is adequate to identify non-conformity of in-process and/or finished product, before it is approved for distribution."²³ Similarly, in a warning letter issued to a Danish firm on September 27, 2006, FDA determined that the manufacturer had failed to identify the "actions needed to correct and prevent re-

currence of non-conforming product" because the "firm's action of testing a limited number of samples of the material upon receipt does not address the unidentified cause of the material nonconformity."²⁴ The manufacturer's response was deemed inadequate because the manufacturer failed to "define how [it] plan[ned] to perform its analysis of rejected" components or offer a plan if the nonconformity was caused by "a reason other than [the identified] problems."²⁵

In preparing a response to an FDA-483, companies should conduct a thorough investigation of the problem identified and provide a complete overview of the areas examined (particularly where no system-wide problem is identified). For example, FDA concluded that a Canadian firm's response was inadequate because the firm had "not implemented any corrective and preventive actions to investigate the cause of [the] problem and prevent its recurrence. The investigation report that was supplied during the inspection is inadequate because it did not scientifically determine the cause of the premature battery failure but simply proposed a fix."²⁶ Of course, identification of the root cause of a problem is not always possible.²⁷ However, where feasible, identifying the root cause allows for more direct verification or validation of the corrective action. Where the root cause for an observed problem is not identified, the response should provide sufficient detail regarding the efforts taken to identify the root cause to assure FDA that the manufacturer is not merely refraining from identifying the root cause in order to avoid having to undertake a difficult field action.²⁸

5. The response should provide specific evidence of the corrective actions taken.

In determining whether to issue a warning letter, FDA considers "whether [sufficient] documentation of the corrective action was provided to enable the agency to undertake an informed evaluation."²⁹ An effective response, therefore, should provide enough evidence of the corrective actions taken to convince FDA that a warning letter is unnecessary. In a warning letter issued on May 16, 2006, to a German firm, FDA noted that the corrective action stated by the manufacturer to correct a failure to adequately establish and maintain procedures for finished device ac-

ceptance could not be confirmed.³⁰ Specifically, FDA stated that "[n]o evidence... was provided, such as a process validation protocol, a process validation report, or chemical residual acceptance levels."³¹ Simply describing the actions taken is not sufficient; additional evidence is always necessary.

Similarly, in a warning letter issued on October 17, 2007, to a Swiss firm, FDA stated that the manufacturer's response to the FDA-483 was inadequate because, although it described in detail the design and development plans it had implemented with regard to its product fixation system, the firm did not provide "appropriate documentation showing that a design and development plan has been established."³² Firms should therefore include copies of all corrective action plans, procedures and protocols in their response to FDA, rather than simply describing such measures.³³

Whenever corrective action is taken, the foreign manufacturer should provide as much documentation as possible to conclusively establish that corrective action has been effected. This documentation should include document control records, training records or even photographic evidence supporting the corrective actions taken. The more documentation that can be provided in a response, the more likely FDA will accept that the corrective action has been implemented and determine that re-inspection is unnecessary.

6. When implementing a new procedure, the response to an FDA-483 should include specific documentation of the training of personnel conducted for the new procedure.

Any time a new procedure is put in place to address an observation in an FDA-483 or warning letter, the firm should provide FDA with documentation of training of personnel on the new procedure. In a warning letter issued to a Canadian firm on Oct. 31, 2007, FDA specifically requested "documentation showing that personnel had been adequately trained," in addition to documentation of the implementation of the new procedure addressing the FDA-483 observation.³⁴ Similarly in a warning letter to a German firm issued on Nov. 17, 2004, FDA notes the firm's response "stated that employee re-training would be conducted in process control, document control, and [medical device re-

Firms in non-English speaking countries should provide full English translations of all documentation submitted to FDA.

porting] procedures ... [but] these procedures and the training records were not submitted in [the firm's] response for [FDA's] review."³⁵ Generally, retraining should be conducted whenever the failure to follow a procedure is observed, even where the procedure is not revised or a new procedure implemented. Documentation of any retraining conducted as part of an action plan to address an observation should be provided in the firm's response to FDA.

7. Provide English translations of all documentation submitted to FDA.

Firms in non-English speaking countries should provide full English translations of all documentation submitted to FDA. A common reason for determining an inadequate response following a foreign inspection is the failure to completely translate the response into English. FDA noted this problem in 12.7 percent of the warning letters for which a manufacturer had submitted an FDA-483 response. Even where a foreign language document is accompanied by a general description of the contents in English, FDA will accept the document for review only if it is accompanied by a full translation. For example, in a warning letter issued on Oct. 11, 2006, to a

Belgian firm, FDA noted that although the manufacturer provided the requested documentation, "an English translation of [the relevant] protocol and test results [was] needed to complete [FDA's] review. Additionally a copy of an internal memo... was also provided; however, an English translation of this memo [was] needed to complete [FDA's] review of this [sic] documents."³⁶ To avoid potential miscommunication, it is important to have any translation prepared and reviewed by technical and regulatory advisors familiar with the FDA regulations and vernacular.

8. Longer-term action plans should be followed up with specific documentation of the completion of the action.

For issues that may take longer to fully address, it is important to provide FDA with notice of the proposed corrective action plan, along with a realistic time frame for its completion. This proposal will not be enough to fully address the issue for FDA, however, and should be followed up with documentation when the action has been completed. If the action will take longer than one to two months, periodic updates on progress also may be necessary. In a warning letter issued Dec. 23, 2003, to a Canadian manufacturer, FDA noted that

the manufacturer put in place a "corrective action plan" to address a particular deficiency.³⁷ However, despite several communications from the manufacturer, the FDA noted in the warning letter that these responses "did not provide documentation to FDA that this plan is completed."³⁸

Available data suggest that FDA takes, on average, 143 days from the close of a foreign medical device inspection to issue a warning letter. Approximately three-quarters of foreign warning letters (73 percent in 2006 and 81 percent in 2007) were issued four months or more following the close of the inspection. In light of this data, manufacturers should not assume that FDA will not issue a warning letter merely because several months have passed without any communication from the agency. Any outstanding corrective action items should be completed, and the results transmitted to FDA in an adequately documented response, as soon as practicable.

It's All in the Details

Manufacturers should correct as many observations as possible before the end of a foreign inspection to ensure that the corrective actions are noted by FDA investigators in their report. Whenever an observation requires additional time to correct, the man-

ufacturer should prepare a well-documented, detailed response to the FDA-483 describing the proposed corrective actions and providing a timeline for the completion of those actions. This response should demonstrate a clear understanding of the cited deficiencies and describe comprehensive and proactive corrective actions aimed at resolving extant problems and preventing their recurrence.

Retaining outside regulatory experts, FDA attorneys or consultants, prior to an inspection may be in a company's best interest since the experts can assess the significance of observations or issues FDA raises on an FDA-483 before the investigation is closed. These experts, attorneys and consultants can then help the company promptly prepare the written response. Manufacturers will be better positioned to avoid a warning letter, and thus the potential disruption of their U.S. marketing by keeping the preceding lessons in mind when preparing their FDA-483 responses. ♦

References

1. U.S. Government Accountability Office, Testimony Before the Subcommittee on Oversight and Investigations, Committee on Energy and Commerce, House of Representatives, Medical Devices: "Challenges for FDA in Conducting Manufacturer Inspections, GAO-08-428T" (Jan. 29, 2008) (statement of Marcia Crosse, director of health care).

2. FDA, "Regulatory Procedures Manual," pages 6-9 (March 2009), available at www.fda.gov/ora/compliance_ref/rpm/pdf/ch9.pdf.

3. 21 U.S.C. § 381(a).

4. See 21 U.S.C. § 331(a).

5. Carolyne Hathaway, John Manthei, and Seth Mailhot, "What You Don't Know Can Hurt You: Understanding the FDA's Foreign Inspection Program, Med. Devices Litig. Rep." (Feb. 4, 2008).

6. Regulatory Procedures Manual, supra note 2, § 4-1-3(1)(a)-(c), available at www.fda.gov/ora/compliance_ref/rpm/pdf/ch4.pdf (stating that in determining whether to issue a warning letter, FDA should generally consider whether "[e]vidence [including evidence provided in FDA-483 responses] shows that a firm, product, and/or individual is in violation of the law or regulations and that failure to achieve adequate and prompt correction may

result in agency consideration of an enforcement action; [t]he violation(s) are determined to be of regulatory significance...; and [t]here is a reasonable expectation that the responsible firm and persons will take prompt corrective action.")

7. Warning letter from FDA to G&B Electronic Designs Limited (Apr. 24, 2007), available at www.fda.gov/foi/warning_letters/archive/s6338c.htm.

8. See *id.*

9. See *id.*

10. Warning letter from FDA to Chien Ti Enterprise Co. Ltd. (Aug. 28, 2006), available at www.fda.gov/foi/warning_letters/archive/g6004d.htm. See also warning letter from FDA to Tyco Healthcare Group (Feb. 25, 2005), available at www.fda.gov/foi/warning_letters/archive/g5229d.htm (stating the firm's "validation study did not identify the [cited] white area or its air handling/HEPA filter equipment as equipment requiring validation and did not include an evaluation to justify why requalification was not necessary").

11. Warning letter from FDA to Nanogen Point-of-Care, Diagnostic Division (July 17, 2007), available at www.fda.gov/foi/warning_letters/archive/s6519c.htm.

12. *Id.*

13. "Regulatory Procedures Manual," supra note 2, § 4-1-3.

14. *Id.* § 4-1-3(2)(d).

15. FDA, "Guide to Inspections of Quality Systems 56" (Aug. 1999), available at www.fda.gov/ora/inspect_ref/igs/qsit/QSITGUIDE.PDF.

16. *Id.* at 56-57.

17. "Guide to Inspections of Quality Systems," supra note 15.

18. Warning letter from FDA to Gynetics Medical Products NV (Jan. 16, 2007), available at www.fda.gov/foi/warning_letters/archive/s6349c.htm.

19. Warning letter from FDA to SagaTech Electronics Inc. (April 7, 2003), available at www.fda.gov/foi/warning_letters/archive/g4027d.htm.

20. *Id.*

21. Warning letter from FDA to ALMO-Erzeugnisse Erwin Busch, GmbH (May 26, 2006), available at www.fda.gov/foi/warning_letters/archive/awl190.htm.

22. *Id.*

23. See *id.*

24. FDA, warning letter issued to Radiometer Medical ApS (Sept. 27, 2006)

available at www.fda.gov/foi/warning_letters/archive/g6156d.htm.

25. *Id.*

26. Warning letter from FDA to ProBed Medical Technologies Inc. (Oct. 31, 2007), available at www.fda.gov/foi/warning_letters/archive/s6573c.htm. See also warning letter issued to Tyco Healthcare Group, supra note 10 (stating "your firm failed to investigate the root cause of high microbial counts noted during the monthly environmental monitoring program although corrective action was taken.")

27. "Guide to Inspections of Quality Systems," supra note 15, at 55.

28. *Id.* at 56.

29. "Regulatory Procedures Manual," supra note 2, § 4-1-3(2)(e).

30. Warning letter from FDA to ESKA Implants GmbH & Co. (May 16, 2006), available at www.fda.gov/foi/warning_letters/archive/g5882d.htm.

31. *Id.*

32. Warning letter from FDA to CoLigne AG Utoquai 43 (Oct. 17, 2007) available at www.fda.gov/foi/warning_letters/archive/s6559c.htm.

33. See also warning letter from FDA to ITO Co. Ltd. (Mar. 7, 2005) available at www.fda.gov/foi/warning_letters/archive/g5237d.htm (illustrating FDA repeatedly asking the firm to submit copies of its methods and procedures for FDA's review.)

34. Warning letter from FDA to ProBed Medical Technologies, Inc., supra note 26.

35. Warning Letter from FDA to Pajunk GmbH (Nov. 17, 2004), available at www.fda.gov/foi/warning_letters/archive/g5173d.htm.

36. Warning letter from FDA to International Brachytherapy s.a. (Oct. 11, 2006) available at www.fda.gov/foi/warning_letters/archive/g6054d.htm.

37. Warning letter from FDA to IND Diagnostic, Inc. (Dec. 23, 2003), available at www.fda.gov/foi/warning_letters/archive/g4451d.htm.

38. *Id.*

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