

WASHINGTON WRAP-UP

Abbott Reinspection Raises Old Issues, New Questions

Despite two years under a consent decree and intensive efforts to comply, Abbott Laboratories has found itself once again in FDA's doghouse.

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It has been more than two years since Abbott Laboratories (Abbott Park, IL) entered into a \$100 million federal court consent decree to correct years of accumulated GMP problems in its diagnostics division. In January 2002, FDA again inspected the facilities. The result was a 23-page, 49-observation Form FDA 483, and signs of a potential standoff with the agency.

A well-placed source familiar with FDA's inspection of Abbott questioned the objectivity of the inspection and the fairness of the observations. This source contended that some of the problems observed were taken out of context. If these apparent problems had been viewed as part of a larger whole, said the source, they would have been fully explained and not seen as problems.

Such contentions are, of course, matters of judgment. It is often hard to second-guess FDA investigators' collective judgments—all the more so when, as in this case, no fewer than eight investigators, some of them specialists, were involved in the inspection.

The November 1999 consent decree under which the inspection was conducted was, at the time, an FDA cause célèbre. It climaxed decades of regulatory jousting with the firm, which top FDA officials saw as having a "hard-case" corporate culture.

The suspicion that the latest inspection could be tinged with politics is not beyond reason. Indeed, it has been reported that Abbott energized the Illinois congressional delegation to put pressure on the agency, in addition to going over FDA's head in a written protest to HHS secretary Tommy Thompson.

Whatever its unseen baggage, the latest FDA 483 echoed some longstanding concerns expressed in the March 1999 FDA warning letter to Abbott that led to the consent decree. These related to Abbott's failure to establish and maintain adequate procedures for implementing corrective and preventive action (CAPA), and failure to perform proper validation and design verification.

Abbott then retained the consulting firm Quintiles Inc., which inspected the company and provided FDA with an audit report certifying that Abbott was meeting the decree's CAPA conditions. An FDA follow-up inspection at that time, like the latest inspection (which lasted 58 working days, from October 10, 2001, until January 18, 2002) continued to document deficiencies with the company's CAPA system.



The decree had provisions for a \$15,000-a-day fine, limited to a maximum of \$10 million, for failure to comply with the CAPA requirements within 120 days. An Abbott spokesman acknowledged in February that fines had been paid, but declined to say how much.

The new FDA 483 contends that validation problems persist at Abbott. In addition to a substantial number of observations involving CAPA, other observations cover such areas as design controls, process validation, purchasing controls, production and process controls, document control, and receiving, in-process, and finished device acceptance.

If FDA's Center for Devices and Radiological Health concurs with the findings of the investigators, what enforcement options does FDA have left, having already gained a federal court consent decree in 1999?

Former FDA district director John Scharmann, who has been closely following the Abbott case, regards criminal prosecution as one very unlikely possibility. A second, and even less likely, remedy, he says, is contempt of injunction. This course of action has been used even less than criminal prosecution.

"In the event that FDA should attempt to use either of these remedies," Scharmann says, "I believe Abbott could make a very good case that it has been working hard to reach compliance. Besides, [Abbott could argue that] 'FDA has permitted us to manufacture 54 medically necessary products during this two-year period under the GMPs in place and we have caused no injury to any consumer'."

Abbott's Utah Facility Receives Warning Letter

In what may be seen as an escalation of FDA's surveillance of Abbott Laboratories in the agency's Chicago district, a January 30, 2002, warning letter from the Denver district documents new problems at an Abbott medical device plant in Salt Lake City. While it is not unusual for FDA to inspect additional company facilities after finding significant GMP deficiencies in one plant, Abbott's case is unique, given the consent decree.

Written 12 days after the close of the Chicago inspection of Abbott's diagnostics facility, the January 30 warning letter could be an effort to prove that the company has not performed an adequate corporate-wide and global assessment of its facilities to ensure each is in compliance with FDA's regulations.

The Utah inspection, conducted last November in the company's hospital products division, found that the division failed to establish adequate CAPA procedures to assure all relevant quality problems are brought to management's attention.

For example, FDA said that Abbott's procedures "do not assure that all sources of quality information are identified, tracked, or trended." CAPA procedures were also found not to include guidelines and time frames for closing corrective action reports. The warning letter cited one corrective action report that was initiated to correct catheter balloon bursts. FDA said there was no evidence this report had been evaluated for efficacy, and that notifications of balloon failure continued to be received after the corrective action.

FDA's inspection also cited the facility for inadequate design controls. FDA noted in particular the firm's distribution of thermodilution (TD) catheters that included new design changes not fully approved or finalized. The warning letter noted that when FDA's investigators asked why a design change was not applied to all TD catheters, they were given two different explanations. One Abbott employee said that "tooling issues somehow prevented implementation," while another employee said that the company "was limited in its ability to manufacture these catheters" and that "the new design was not to be manufactured until new equipment was purchased to increase production."

FDA reminded the company that "it is essential that if your firm determines that a design change is warranted, the decision to implement or not to implement must be made using a risk-based assessment. That is, a risk-based assessment of the impact on patients' health should be performed prior to determining whether or not to implement the change."

More Time for Disposables Reprocessors

FDA is extending its enforcement deadline for Class II 510(k) single-use devices (SUDs) to August 14,

according to a February notice on FDA's Web site. The agency said it had agreed to extend the deadline for reprocessors who submitted a 510(k) by August 14, 2001, did not receive a "not substantially equivalent determination" decision, and provided timely responses to any requests information.

The notice also said that FDA would actively enforce its premarket approval requirements for Class III SUDs on February 14, 2002. The agency also may take enforcement action against any Class I SUD if an application has not been submitted by that date, or if the device has not received marketing clearance by August 14, 2002.

Blood Pattern Test for Disease

Protein patterns in a patient's blood serum may reflect the presence of disease, FDA said in a February press release. Together with Correlogic Systems Inc. (Bethesda, MD), FDA and the National Cancer Institute (NCI) conducted the research leading to this finding as part of the FDA/NCI Clinical Proteomics Program.

According to FDA, scientists were able to use serum proteins to detect ovarian cancer, even at early stages, using blood obtained from a fingertip and processed with a 30-minute test. Using an artificial intelligence program that identifies key protein patterns from among thousands, the test could distinguish accurately between patients with the cancer and those unaffected. The agency said this new concept is potentially applicable to any type of disease.

This finding is particularly important, FDA said, because researchers were able to "correctly identify, in a small sample of patients, all stage I ovarian cancer cases. Currently, more than 80% of ovarian cancer patients are diagnosed at a late clinical stage and have a 20%-or-less chance of survival at five years. In contrast, the 20% of women diagnosed with early-stage disease have an excellent prognosis, with over 95% alive at five years after diagnosis."

Dental Amalgams Get FDA Attention

FDA will uniformly regulate dental mercury, amalgam alloys, and preencapsulated dental amalgams, and will propose a labeling guidance to reduce allergic reactions from restorative materials, the agency said in a February 7 consumer update. The agency released the update in response to recent public concerns about the safety of amalgams. It said that while the U.S. Public Health Service and other organizations are investigating the safety of the substances, "no valid scientific evidence has ever shown that amalgams cause harm to patients with dental restorations."

FDA said it plans to make available a labeling guidance that will propose that the products be labeled with all ingredients, in descending order of weight by percentage. The labeling would include lot numbers, list appropriate warnings and precautions, and provide handling instructions and expiration dating. FDA said it is aware that some manufacturers now provide some of this material, primarily contraindications, in their labeling of dental amalgams sold outside of the United States. Any manufacturer wishing to add such information to U.S. labeling will be required to submit a new marketing application with data supporting such a change.

Device-Tracking Regulation

Beginning May 9, medical device tracking will be required only when FDA issues an order to a manufacturer after determining the device meets new criteria imposed by the FDA Modernization Act. According to a final rule published on February 8, FDA can only require a manufacturer to implement a method of tracking a Class II or III device if the failure of the device could have severe adverse health consequences, or if the device is an implantable and is expected to remain in the body for more than one year, or if the device is used outside of a device-user facility for life-sustaining or life-supporting purposes.

FDA says that it reserves the right to waive tracking for any device that meets these criteria. The final rule mentions that the agency has rescinded tracking orders for 14 types of devices, including intraocular lenses and arterial stents, even though they met the criteria. In deciding whether to waive device tracking, FDA says it will also consider "nonbinding" factors, such as the likelihood of sudden, catastrophic failure; the likelihood of significant adverse clinical outcomes; and the need for prompt professional intervention.

Types of devices for which FDA has recently ordered tracking under the FDAMA criteria include duramater devices, stent grafts that treat abdominal aortic aneurysms, replacement heart valves, temporomandibular joint prostheses, cardiovascular permanently implantable pacemaker electrodes, and continuous ventilators.

Device-tracking records that manufacturers are required to maintain will now allow patient information to be omitted when a patient has decided not to release such information. This allows device tracking to conform to patient privacy language included in FDAMA.

The final rule can be viewed at

http://www.fda.gov/OHRMS/DOCKETS/98fr/00n-1034_nfr0001.pdf.

Medical Device Broadcasts

FDA has posted on its Web site a patient-safety news page that offers information and links about its televised series of information programs for healthcare personnel, which is carried on satellite broadcast networks. The monthly series is aimed at hospitals and other medical facilities, and features information on new medical devices, FDA safety notifications, and ways to protect patients when using medical devices.

The Web site page contains the text of each broadcast and links to relevant information on each story. It also provides instructions on purchasing videotapes of previous broadcasts. The new page can be accessed at <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfTopic/psn/index.cfm>.

IVD Workshop Will Address 510(k)s

CDRH and the Association of Medical Diagnostic Manufacturers are cosponsoring an in vitro diagnostic 510(k) workshop April 23–24 in Rockville, MD. The workshop is intended for individuals who are interested in learning more about putting together 510(k) applications for IVD products. For more information, contact Dave Lyle at 301/594-3084.

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