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The Special Counsel

September 29, 2015

The President
The White House
Washington, D.C. 20500

Re: OSC File No. DI-11-3325

Dear Mr. President:

Pursuant to 5 U.S.C. § 1213(e)(3), enclosed please find an agency report and a supplemental agency report based on disclosures made by a whistleblower at the Department of Health and Human Services (HHS), U.S. Food and Drug Administration (FDA), Silver Spring, Maryland. The whistleblower, who chose to remain anonymous, alleged that FDA employees responsible for reviewing and approving medical devices violated agency regulations and created a substantial and specific danger to public health and safety by approving several different types of colonography devices for use in general population screening. The whistleblower further alleged that FDA employees responsible for reviewing and approving medical devices violated agency regulations and created a substantial and specific danger to public health and safety by ignoring agency device review protocols and approving the use of a Carestream Health Inc. (Carestream) Digital Mammography device for the screening and diagnosis of breast cancer.

The agency report and supplemental report did not substantiate the whistleblower's allegation that FDA employees acted improperly in approving several different types of colonography devices for use in general population screening or in approving the use of a Carestream Digital Mammography device for screening and diagnosing breast cancer. However, as a result of the investigation, the agency took steps towards making the medical device premarket approval process more transparent, predictable, and consistent. These efforts included more than 35 new initiatives designed to strengthen device review procedures and ensure the creation of a complete administrative file documenting the deliberative process concerning premarket decisions and the balance of device benefits versus risks. In addition, the agency adopted procedures to address internal differences of professional opinion, as well as for documenting associated scientific, clinical and regulatory findings, perspectives and opinions. The whistleblower declined to file comments in response to the reports. Based on my review of the original disclosure and the agency's report and supplemental report, I have determined that the reports contain all of the information required by statute and that the findings appear to be reasonable.

The whistleblower's allegations were referred to then-Secretary of HHS Kathleen Sebelius, to conduct an investigation pursuant to 5 U.S.C. § 1213(c) and (d).[1] The Secretary referred the allegations to the HHS Office of Inspector General (OIG) for investigation. The OIG review was limited to the question of whether the administrative files for the devices in question contained the documentation that should reasonably be included in the file, and to identifying information in the administrative files relevant to FDA's decision to approve or clear the device for screening asymptomatic patients. Citing its lack of scientific expertise, the OIG declined to address the aspects of the whistleblower's allegations requiring an assessment of FDA's reliance on certain clinical data and the relative safety of the medical devices.

Consequently, the Secretary tasked the Commissioner of Food and Drugs with investigating the allegations and reviewing the OIG's findings. On October 1, 2012, the Secretary submitted the agency's report on the whistleblower's allegations to the U.S. Office of Special Counsel (OSC). On May 9, 2014, the agency submitted a supplemental report to OSC. As required by 5 U.S.C. § 1213(e)(3), I am now transmitting these reports to you.

I. Improper Regulatory Review Procedures and Clearance of CT Colonography Devices

A. The Allegations

The whistleblower explained that the FDA is responsible for reviewing the safety and effectiveness of medical devices prior to their introduction into the market. Under 21 C.F.R. § 860.7, the FDA must consider in its review the intended use of a device and must rely only on valid scientific evidence to make its determination as to safety and effectiveness. Pursuant to 21 C.F.R. § 360(f), all devices not introduced for commercial distribution prior to May 28, 1976, are considered Class III devices, excluding those devices that are substantially equivalent to another device within the same type.[2] A device is considered substantially equivalent to a prior approved, or "predicate," device

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[1] The Office of Special Counsel (OSC) is authorized by law to receive disclosures of information from federal employees alleging violations of law, rule, or regulation, gross mismanagement, a gross waste of funds, an abuse of authority, or a substantial and specific danger to public health and safety. 5 U.S.C. § 1213(a) and (b). OSC does not have the authority to investigate a whistleblower's disclosure; rather, if the Special Counsel determines that there is a substantial likelihood that one of the aforementioned conditions exists, she is required to advise the appropriate agency head of her determination, and the agency head is required to conduct an investigation of the allegations and submit a written report. 5 U.S.C. § 1213(c). Upon receipt, the Special Counsel reviews the agency report to determine whether it contains all of the information required by statute and that the findings of the head of the agency appear to be reasonable. 5 U.S.C. § 1213(e)(2). The Special Counsel will determine that the agency's investigative findings and conclusions appear reasonable if they are credible, consistent, and complete based upon the facts in the disclosure, the agency report, and the comments offered by the whistleblower under 5 U.S.C. § 1213(e)(1).

[2] Devices are categorized into three classes: Class I, Class II, and Class III, with Class III devices requiring the most stringent review process. 21 C.F.R. at §807.100(b)

when the new device has the same intended use and technological characteristics as the predicate device. If it has different technological characteristics from the predicate device, the manufacturer must submit data showing that it is as safe and effective as the predicate device.[3]

When reviewing devices for substantial equivalence, the FDA uses the 510(k) review process. If substantial equivalence is found, the agency provides clearance of a premarket notification submitted by the device manufacturer. This "clearance order" allows introduction of the device to the market, but does not constitute FDA "approval" of the device. Rather, approval of a Class III device is achieved through the Premarket Approval (PMA) process, in which the FDA approves a premarket application by the device manufacturer prior to the device being marketed to the public. The PMA process requires submission of valid scientific evidence of the safety and effectiveness of the device.[4] A comparison of the new device against a predicate device is not required. The whistleblower asserted that if an application is submitted for a device under 510(k), but it is determined that the device is not substantially equivalent to a previously approved device, the device should be assessed using the more rigorous PMA approval process.

Regardless of the method of approval used, the FDA is required to fully document each significant decision that is made in the review process. 21 C.F.R. § 10.70. Section 10.70 requires that the FDA employees responsible for handling 510(k) and PMA submissions insure the completeness of the matter's administrative file. This includes appropriate documentation for the basis of the decision, recommendations and decisions of individual employees, and other information deemed necessary. In addition, each written document must be dated and signed by the author, and documents not contained in the file have no status or effect.

The whistleblower alleged that in the process of conducting a review of "premarket notification submission K083548[5]," it was discovered that the device, a computerized tomography (CT) image analysis software package manufactured by General Electric Healthcare (GEHC or GE), had a new intended use compared to its predicate device, K041270. According to the whistleblower, when a new intended use for a device is identified in comparison to a predicate device, the FDA reviewers should instead assess the device using the more stringent PMA review process. The whistleblower alleged that because the PMA process was not used, several devices were improperly approved for use as screening tools on asymptomatic patients, and a large segment of the population could be exposed to unnecessary CT scans, with the potential to cause cancer.

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[3] *Id.*
[4] 21 C.F.R. § 860.7 (2010).
[5] Devices for which a 510(k) submission has been made are assigned a six-digit identification number beginning with K. Devices which have been cleared by the FDA for entrance into the market are maintained in a searchable online database found at http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm, last visited September 17, 2013.

Specifically, the whistleblower disclosed that in its 510(k) application, GEHC predicated clearance of K083548 upon the FDA's prior clearance of another GEHC image analysis software package, K041270, also known as CT Colonography II. K041270 was cleared by the FDA for screening a colon to detect polyps, masses, cancers, and other lesions. In its subsequent application for K083548, GEHC proposed adding language to the previously cleared device's Instructions For Use (IFU) indicating that the new device, known as CT Colonography II (Screening), could be used to screen asymptomatic patients age 50 and under, and that patients found to have actionable lesions should be referred for follow-up treatment. According to the whistleblower, the lead reviewer, Lauren Hefner, stated that questions about the change to the device's IFU would have been appropriate during the review of the predicate device. However, Ms. Hefner found that because the predicate device was approved, she had no grounds to continue an inquiry into K083578, and determined that it was substantially equivalent to the predicate device. According to the whistleblower, although K083548 ultimately was *not* cleared by FDA, applications for several similar devices submitted before and after K083548 were cleared for use with CT scanners.

For example, the whistleblower noted that a similar device manufactured by Viatronix, Inc., K040126, was considered during the 510(k) review of K085348. The whistleblower disclosed that in its application for K085348, GEHC stated that it reviewed the clearance for K040126 and on that basis chose to use the 510(k) review process for its new device. However, the whistleblower explained that during the review of K083548, it was discovered that the administrative file for K040126 did not contain full documentation of the clearance decisions made for the device and did not show that K040126 was cleared by the FDA to perform screening of asymptomatic patients for colon cancer. The whistleblower noted that the IFU for K040126 stated, "The Viatronix V3D Colon is a system for the display and visualization of 3D and 2D medical image data of the colon derived from DICOM 3.0 compliant CT and MR scans, for the purpose of patient screening for detection of colon cancers, polyps, masses, and other lesions."

The whistleblower explained that the FDA has never cleared or approved a CT scanner for use in screening of asymptomatic patients of any age. The whistleblower contended that because the FDA has never cleared a CT scanner for use in screening asymptomatic patients, the phrase "patient screening" in K040126's IFU could not refer to general population screening, but to screening and diagnosis of symptomatic patients only. Thus, the whistleblower alleged GEHC's reliance on the approval of K040126 as a device for use in asymptomatic patients was misplaced.

In addition, the whistleblower contended that the administrative file for K020658, the predicate device for K040126, contained documentation showing that FDA's original interpretation of "patient screening" was screening of an individual patient's colon, not screening of a population of patients, but that this was ambiguous in the device's

labeling. The FDA requested, in the absence of data supporting the device's use for population screening, that Viatronix amend the IFU to show that the device was not cleared for such a use, which Viatronix did. However, the whistleblower contended that this was changed again following Viatronix's submission of an independent clinical study comparing the safety and effectiveness of the company's device to that of endoscopic colonoscopy. Following a review of that study, the FDA allowed Viatronix to amend the original labeling for the device, such that it could be labeled for use in population screening.

The whistleblower contended that this clearance was in error for a number of reasons. First, the manufacturer failed to submit a new 510(k) application for agency review, so no regulatory submission was before the agency at the time the final labeling change was made. Additionally, the publicly available IFU cleared by the FDA for the device does not state that it was cleared for "colon cancer screening." The whistleblower also noted that the clearance did not take into account that the FDA had neither cleared nor approved any CT scanners for this use.

The whistleblower alleged that the file supporting the clearance of K040126 was inadequate and in violation of 21 C.F.R. § 10.70. The whistleblower alleged that in the administrative file for K040126, Dr. Loren Zaremba, lead reviewer, noted that the intended use of the new device was the visualization of colons from CT scans, and that an independent study concluded that the predicate device was safe and effective. This led to FDA's clearance of K040126 for population screening.

The whistleblower contended that this clearance was also in error, because there is no signed review memorandum or similar documentation showing an analysis of the predicate device. The whistleblower alleged that this is a violation of § 10.70, which requires that appropriate documentation for decisions made by FDA employees must be maintained in a file and that written documents within the file must be signed by the author. The whistleblower noted that the lack of documentation in this case is of particular concern because the devices were cleared for a new use that could have a profound effect on patient health.

Several other devices have also been cleared with ambiguous language in their IFUs. These include: K043194, Voxar Ltd.; and K083423 and K042674, MedicSight PLC. All of these devices have been marketed by their manufacturers as cleared for the purpose of screening asymptomatic patients. The MedicSight device was also the basis for the clearance of another device manufactured by iCAD, Inc., K091529, which claimed substantial equivalence with MedicSight's K042674. K042674 was found to be substantially equivalent with K083423, which is marketed for screening of asymptomatic patients. Thus, it is possible that K091529 may also be marketed for such screening. Similarly, Siemens AG Medical Solutions, K042605, was used as a second predicate

device for the iCAD, Inc., K094529 submission, and also has IFU that are silent on screening for asymptomatic patients.

The whistleblower alleged that there is insufficient data showing that the use of CT technology for population screening outweighs the risks. Rather, for asymptomatic patients, regular and/or repeated CT screening of the colon is unlikely to identify a serious disease, and the potential harm to the patient may outweigh the presumed benefit. The whistleblower noted that FDA's own website references an article about full-body CT scans that states, "CT screening of high-risk individuals for specific diseases such as lung cancer or colon cancer is currently being studied."[6]

B. The Agency Report

i. OIG Review of CT Colonography Devices

The agency submitted as part of its report the OIG's review of the administrative files for the Carestream and colonography devices. With regard to the colonography devices, the OIG reviewed the administrative files for only those submissions that were approved for use by FDA, namely K040126 (Viatronix). The OIG noted that it also reviewed the file for K020658 for context in relation to K040126 and found that at least one document was missing from each of the reviewed files.

The OIG created a list of items that should reasonably be included in an administrative file, based upon its review of relevant regulations, prior OIG 510(k) reviews, administrative files, and input from FDA officials. Briefly, the list includes: documentation of reviewer analysis, including sponsor-submitted additional information; meeting minutes and correspondence with sponsors and consultants, such as contents and dates of phone calls and email chains; and other standard documents including approval orders, clearance letters, and user fee forms. The OIG was not able to identify missing documents from administrative files if the documents were not referenced elsewhere in the file.

The OIG found that in the 2002 file for K020658, the Reviewer Decision Flowchart, a visual representation of the logic used to clear a device, was not completed, signed, or dated. Also missing from the K020658 was an email between the FDA and the device sponsor, Viatronix. The OIG found that the FDA had determined the original device IFU was ambiguous and required the sponsor to change the wording. The file contained a document stating that the FDA emailed the subsequent approval to Viatronix, but that email was not in the file. The FDA's acknowledgement letter to Viatronix was in the file but was not signed.

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[6] http://www.fda.gov/Radiation-EmittingProducts/RadiationEmittingProductsandProcedures/MedicalImaging/MedicalX-Rays/ucm115340.htm, last accessed September 17, 2013.

With regard to the 2004 file for K040126, the OIG found that the reviewer memorandum was missing from the file. The memorandum documented the review of new evidence resulting in a change to the device's IFU. The OIG found the memorandum, unsigned, in the administrative file for K020658.[7] The OIG further found that some review documentation was not properly signed and dated, including the screening checklist, decision flowchart, and FDA Acknowledgement Letter. The file was also reviewed for information related to the decision to clear the device for use on screening of asymptomatic patients, determining that the IFU was found to encompass such screening. The report notes that devices such as K040126 are used in conjunction with CT scanners, and that the IFU for CT scanners are generally broad. Thus, sponsors of applications for CT scanners have not specifically addressed the use of CT scanners in asymptomatic patients. The OIG referenced the FDA's website, which states, "No data have been presented to the FDA to demonstrate that [CT scanners] are effective for screening...." Further, the FDA advised OIG that no manufacturer of CT scanners had submitted an application to clear them specifically for use in asymptomatic patients. However, OIG made no determination as to whether the devices were appropriately approved or cleared.

ii. Commissioner of Food and Drugs Review

The agency also submitted a report by the FDA Commissioner (the Commissioner's report) regarding the appropriateness of the approval process for the colonography devices. The Commissioner's report confirmed that in 2002, the FDA cleared the Viatronix 510(k) submission for K020658, the predicate device to K040126. The original IFU for K020658 stated that the device was for the purpose of patient screening. Following the clearance of the device, the FDA issued a letter to Viatronix and companies with similar device claims informing them that the phrase "patient screening" was ambiguous. The FDA determined that the IFU could be read to mean "population screening," for which the FDA did not believe that K020658 was cleared. Thus, the FDA requested that "patient screening" be removed from the IFU, and Viatronix and other manufacturers complied by substituting the phrase "screening a colon."

In 2003, Viatronix submitted a large clinical study to the FDA supporting the use K020658 for screening symptomatic patients. The study found that CT colonography compared favorably with optical colonoscopy for screening of symptomatic patients. FDA determined that the study demonstrated the safety and effectiveness of the device, and thereafter, cleared a 510(k) allowing Viatronix to amend its indication statement to include the phrase "patient screening."

[7] The OIG explained that Viatronix requested a change to the IFU for K020658 in 2002. The review of that change was completed in 2003, and the FDA informed Viatronix of the review and invited the sponsor to submit a new 510(k) in order to official change the IFU. The new 510(k) submission was received by the FDA and cleared in 2004.

The Commissioner's report explained that in 2009, GE submitted a 510(k) application for its own CT colonography device for asymptomatic screening. The review of that application found that the Viatronix device was cleared for asymptomatic screening and was appropriately cited by GE as a predicate device to its own device. The Commissioner's report acknowledged that during the review of the GE device, two of the reviewers raised concerns about the safety of using the devices for screening of asymptomatic patients, arguing that the Viatronix device was not cleared for such a purpose. The Commissioner's report noted that the FDA reviewed whether the switch to asymptomatic screening constituted a new intended use, but concluded that the original Viatronix device was an appropriate predicate for asymptomatic screening, and the approval did not need to be rescinded.

At that time, the Office of Surveillance and Biometrics (OSB) also evaluated the safety and effectiveness of the CT colonography devices, including reviewing public clinical data on the effectiveness of the device, an assessment of the radiation risk associated with the devices, and a comparative assessment of the risks of perforation associated with colonography and colonoscopy procedures. The OSB found that CT colonography was comparable in effectiveness to colonoscopy, with minimal radiation risk. The OSB thus unanimously determined that the benefits of CT colonography were significant and the radiation risks were justified. It was noted, however, that the risks could be reduced through various measures and recommended that the 510(k) review team pursue such reduction measures. The Commissioner's report stated that in 2010, the FDA launched an initiative to reduce unnecessary radiation exposure from medical imaging, including CT scans. The Commissioner's report further stated that FDA is currently working with manufacturers to develop devices that use smaller doses of radiation and is developing dose reference standards for the minimum radiation dose necessary to generate images of sufficient quality.

The Commissioner's report stated that CT scanners are generally cleared for broad diagnostic and therapeutic uses, which are not specifically listed in each device's labeling. According to the Commissioner's report, software devices such as the ones at issue have been cleared for use in diagnostic evaluation of the colon with CT images since the 1990s. While FDA has not cleared CT scanners themselves for screening of asymptomatic patients, the associated software devices have been cleared for such use. Thus, the Commissioner reviewed whether, under 21 U.S.C. § 360c(i)(1)(A), the CT scanners must be considered as predicate devices to the devices at issue. The OIG determined that CT scanners were not listed as predicate devices in Viatronix's 510(k) submissions and that the manufacturer and the FDA reviewers considered prior software devices, and not the CT scanners, as the appropriate predicate devices. Thus, the FDA Commissioner found that it is not relevant whether CT scanners were cleared for screening of asymptomatic patients, because they were not appropriate predicate devices to the devices at issue.

Further, the Commissioner's report reiterated that a change to an IFU statement does not necessarily indicate a new intended use for the device. Pursuant to 21 C.F.R. § 807.92(a)(5), for a manufacturer to show that a change to the IFU is not a new intended use, the 510(k) submission must show that the differences are not critical to the intended use of the device and do not affect the safety and effectiveness of the device when used as labeled. FDA's own guidance provided a broad standard for determining a new intended use, with general criteria including physiological purpose, the condition to be treated, use by a professional or lay person, the part of the body involved, and the frequency of use.

The Commissioner's report clarified that the standards for assessing new intended uses are flexible to allow for decision-making based on scientific expertise and judgment. Thus, the investigation evaluated the approach the FDA took, which reviewed several devices contemporaneously with the subject devices, in order to determine what consideration was given to the question of changing from a diagnostic use to an asymptomatic use. With regard to the 2004 Viatronix submission, the investigation found that the lead reviewer based his conclusion that there was no new intended use in part on the large clinical study submitted by the manufacturer. The reviewer found the study adequate to support the change in the IFU, and concluded that the device was substantially equivalent to the predicate device. The 510(k) submission was cleared, permitting the change.

According to the Commissioner's report, the record related to the GE device 510(k) submission also reflected a review of whether the change in the IFU constituted a new intended use. In that case, the lead reviewer determined that the predicate Viatronix device was properly cleared and that the GE device appropriately cited it as a predicate device. Because, as described above, there was some dissent regarding this determination, the director of the Biophysics Laboratory was asked to conduct a review as well. Upon review, the director agreed with the lead reviewer's determination that there was no new intended use. Further, the Commissioner's report noted that FDA reviewed the risks and benefits of the device, including Viatronix's scientific review of the clinical study and an evaluation of available evidence of radiation risks. The Commissioner's report found that following a meeting of the interested parties and a review of the regulatory history of the issues surrounding CT colonography, the Viatronix device was determined to be an appropriate predicate device, and the decision to clear 510(k) submissions for asymptomic screening was deemed appropriate. Further, the Commissioner's report noted that a similar determination was made in a recent analogous case regarding colonoscopes, which themselves are not indicated for asymptomatic screening.

The Commissioner's report also explained that in December 2011, the FDA issued new draft guidance on evaluating substantial equivalence. The new guidance is more specific about when a new IFU may create a new intended use and clarifies that

changes from diagnostic to screening indications warrant particular attention in evaluating safety and effectiveness. The Commissioner concluded in the report that the decisions concerning the Viatronix and GE devices are consistent with this draft guidance.

The Commissioner reviewed the OIG's determination that missing or unsigned documents do not necessarily indicate that the devices at issue were improperly cleared. The FDA CT report concurred with the OIG's finding that the files lacked completeness, in possible violation of 21 C.F.R. § 10.70, but found that the violation does not create a basis to invalidate the clearances of the devices. Rather, the Commissioner's report found that the errors in the files were not substantial and did not call into question the legal or scientific bases for clearing the 510(k) submissions. However, according to the Commissioner's report, the FDA recently issued standard operating procedures for compiling premarket submission administrative files, and the Commissioner asked the FDA to correct the errors that the OIG's review discovered.

The Commissioner also investigated the allegation that the improper clearance of the devices at issue posed a health risk to the population due to radiation exposure. In the investigation, the Commissioner reviewed evidence of colorectal cancer rates in the United States, recommendations for universal colorectal screening for those over age 50, the low rates at which such screening is occurring, and the role of CT colonography in screening. The Commissioner also reviewed the agency's method of evaluating safety and effectiveness in 2009 and the claim that use of CT colonographies could increase the incidence of colon cancers annually. The Commissioner's report also recommended that the Commissioner hold an advisory committee meeting to consider current data on the risks and benefits of the devices.[8]

The Commissioner's report noted that despite the fact that colorectal cancer is the second leading cause of cancer deaths in the United States, and increased public attempts to encourage screening for adults between the ages of 50 and 75, only about 60% of Americans who meet the criteria for screening are screened. According to the Commissioner's report, one reason for the low screening rates is the discomfort associated with traditional colonoscopy. Unlike colonoscopy, CT colonography is non-invasive, does not require sedation, has no recovery time, and has few side effects other than the risk from radiation. The report notes that efforts to reduce radiation exposure are ongoing, and studies have shown that CT colonography has a high rate of sensitivity and acceptable rate of specificity for the most important types of polyps. Although CT

[8] On September 9, 2013, the agency convened a joint meeting of the Gastroenterology-Urology Panel and the Radiological Devices Panel of the Medical Devices Advisory Committee to discuss the risks and benefits of CT colonography screening in asymptomatic patients. The meeting included seven expert presentations, which the panel considered along with presentations delivered at an open hearing and 20 papers submitted prior to the meeting. After deliberation, the panel concluded that given the identified risks and benefits, CT colonography should be one option for screening for colorectal cancers in asymptomatic patients. Information about the panel's meeting and conclusions can be reviewed at: http://www.fda.gov/newsevents/meetingsconferencesworkshops/ucm366949.htm.

colonography does require follow-up colonoscopy if suspicious polyps are identified, it can also detect other potentially serious findings in surrounding organs. In addition, other available technologies have similar issues to CT colonography. For example, barium contrast enemas deliver a comparable dose of radiation to CT colonography. Thus, the agency notes that due to the low rate of colonoscopy screening, having other safe and effective screening options, such as CT colonography, is important to public health.

The Commissioner's report also addresses the OSB's evaluation of the risks and benefits of the CT colonography, as discussed above. The report reiterates the finding that the OSB's review in 2009 was carefully conducted and notes that an initiative was put in place shortly after the review to reduce unnecessary radiation exposure. The report acknowledges the OSB's determination that the benefits of CT colonography outweighed its risks when used to screen asymptomatic patients.

The Commissioner also reviewed the whistleblower's contention that the 2009 decision by the Centers for Medicare and Medicaid Services (CMS) not to cover CT colonography for Medicare patients is evidence that research does not support its use in screening applications. The Commissioner's report clarifies that the question before CMS was not analogous to the question before the FDA in clearing the subject devices. For example, CMS was looking for evidence of the performance of CT colonography in patients 65 years and older, and CMS noted in its decision that populations served by other health plans are younger than the Medicare population, and thus findings from studies showing that CT colonography is comparable to colonoscopy would be more directly applicable to those plans. The Commissioner's report noted that many medical groups and insurers have reached similar conclusions to the FDA on the use of CT colonography, including Kaiser Permanente, Blue Cross/Blue Shield, and a group of stakeholders, including the American Cancer Society, which issued a joint guideline, along with the US Multi-Society Task Force on Colorectal Cancer and the American College of Radiology. The Commissioner's report acknowledged that some groups have found there is still insufficient information to support the use of CT colonography, but noted that the research is generally three to four years old and that recent updates issued by the American Gastroenterological Association show results for Medicare-age patients that are similar to general screening populations.

Further, the Commissioner's report stated that it found no significant basis for the whistleblower's estimate that the use of CT colonography could lead to an increase of 7,000 colon cancers annually. The Commissioner noted that the whistleblower did not state the assumptions underlying the estimate or present scientific evidence to support the contention, making it difficult to provide a response. The Commissioner's report found that the estimate was not based on a fair assessment of the relevant factors, including the number of colon cancers potentially prevented by early detection. The agency indicated that it is not aware of any outside scientists or groups who have suggested that the use of CT colonography would increase colon cancer. The Commissioner's report noted that a

recent risk-benefit analysis comparing the risk of cancers to the benefit of prevention found that CT colonography could prevent between 24 and 35 times more colorectal cancers as total cancers induced by radiation.

II. Improper Regulatory Review Procedures and Approval of Carestream Digital Mammography System

A. The Allegations

The whistleblower alleged that FDA managers ignored review team concerns that Carestream failed to provide adequate analytical data in support of its PMA application for a Digital Mammography device intended for use in the screening and diagnosis of breast cancer. FDA managers, according to the whistleblower, circumvented the FDA's prescribed review and approval procedures and approved Carestream's application despite concerns the review team repeatedly raised that the manufacturer failed to empirically refute a trend questioning the effectiveness of the Carestream device in detecting cancers that appear as microcalcifications in the breast. The whistleblower contended that the improper approval of the Carestream Digital Mammography device poses a significant public health risk given that approximately half of all breast cancers appear as microcalcifications on mammograms. The use of this device in the routine screening for breast cancers may, according to the whistleblower, lead to a significant increase in the misdiagnoses of or failures to diagnose breast cancers that appear as microcalcifications.

i. Carestream's Application

On July 28, 2008, Carestream submitted PMA P080018, for a Digital Mammography device intended for use in the screening and diagnosis of breast cancer. Rather than using standard film, this particular device consisted of a thin digital detector "plate" about the same size as a piece of film, but thicker, that is made of material that absorbs X-rays. The plate fit into standard X-ray film cassettes that are used for film mammography. However, rather than taking an exposed film into a darkroom for developing in chemical tanks, the imaging plate is run through a special laser scanner that reads and digitizes the image. This technology is different than the technology used in digital cameras and in many other digital mammography devices.

As part of the clinical trial for this submission in support of their PMA application, patients without cancer (n = 150 patients) and patients with cancer (n = 50 patients) were imaged using both the new digital mammography device and conventional film mammography (the standard of care). Two types of comparisons were then made:

- Sensitivity and Specificity Analysis: All cases were interpreted independently by a group of radiologists to determine if cancer was present or absent. The results

showed that the new device was slightly less sensitive than conventional film for cancer detection and that the new device had slightly fewer false positive exams than film. These differences were deemed not statistically significant.

- Comparative Features Analysis: In this analysis, all of the cancer cases, and a smaller number of non-cancer cases, were compared side-by-side primarily to determine whether the new device could reveal cancers as well as film (or better; or worse).

ii. The FDA's November 24, 2008 Major Deficiency Letter

On November 24, 2008, the FDA sent a Major Deficiency Letter (the November Deficiency letter) to Carestream. The letter questioned the validity of the methodology Carestream used to perform the Comparative Features Analysis. The FDA requested that Carestream repeat the Comparative Features Analysis using a valid methodology.

iii. Carestream's Response to the November Deficiency Letter

On January 21, 2009, Carestream responded to the Major Deficiency letter. Instead of repeating the Comparative Features Analysis using a valid methodology as the FDA requested in the November Deficiency Letter, Carestream performed a "post-hoc sub-analysis" of their original data (*i.e.*, an "after-the-fact" analysis performed on only part of the original data). According to the whistleblower, the data Carestream analyzed pursuant to the post-hoc sub-analysis was not representative of a typical screening population. Rather, the whistleblower asserted that the size of the cancers that appeared as calcifications in the analyzed subset was much larger than normal. The whistleblower contended that the larger the size of a cancer, the easier it is to detect and, when testing a new device for safety and effectiveness, it is important to determine whether or not the device can adequately detect and characterize the smaller, more difficult to detect cancers. The whistleblower explained that it is not adequate to test a device using primarily "easy cases." Furthermore, the sub-analysis utilized a much smaller number of cases, making a meaningful statistical analysis essentially impossible. Even ignoring the flawed methodology, the results of the post-hoc sub-analysis revealed a "strong trend" suggesting that the Carestream device might be inferior to conventional film mammography for the detection of cancers that appear as calcifications.

iv. The April 9, 2009 Not Approvable Letter

Following a review of the Carestream response, the FDA review team unanimously recommended the issuance of a Not Approvable letter to Carestream based on Carestream's failure to perform a new Comparative Features Analysis as requested by the FDA. According to the whistleblower, this decision was also based on the fact that the new data analysis that Carestream submitted raised serious concerns regarding the

device's effectiveness for detecting cancers that appear as microcalcifications in the breast.

On April 9, 2009, pursuant to 21 C.F.R. § 814.44(f), the FDA sent a Not Approvable letter (April Not Approvable letter) to Carestream. This letter explained that analysis of the limited data provided by Carestream revealed a trend indicating that the Carestream device may be inferior to film mammography for showing cancers that appear as microcalcifications, and that this was "clinically concerning." The April Not Approvable letter again informed Carestream that their original Comparative Features Analysis was not valid and that a new Comparative Features Analysis must be performed.

v. Carestream's Response to the April Not Approvable Letter

In June 2009, Carestream sent an appeal letter to the FDA requesting "reconsideration" of the decision set forth in the April Not Approvable letter. In September 2009, Carestream received notification that, after reconsideration of FDA's Not Approvable decision, the decision was upheld. In late September 2009, Carestream submitted a response to the April letter. According to the whistleblower, rather than performing a new Comparative Features Analysis employing a valid statistical methodology as instructed by the FDA in the April Not Approvable letter, Carestream provided yet another post-hoc sub-analysis of the data in the original PMA submission.

vi. Review Team Response

In mid-January 2010, the Radiological Devices Branch was moved from the Office of Device Evaluation (ODE) and was subsumed by the Office of In-Vitro Diagnostic Devices (OIVD). In late January 2010, the review team completed their review of Carestream's September 2009 response to the April Not Approvable letter. The team determined that Carestream's new post-hoc sub-analysis was flawed and invalid and that even the limited results Carestream presented continued to raise serious concerns that the device might be inferior to film mammography for detecting cancers that appear as microcalcifications on mammograms.

The review team met several times in January and February 2010 and discussed how to respond to the September 2009 Carestream submission. The review team considered the possibility of issuing a second Not Approvable letter, as well as the possibility of requesting additional analyses of the existing data. Finally, the review team, according to the whistleblower, considered obtaining the actual images from the Carestream study and having the FDA design a new valid Comparative Features Analysis. The review team contemplated asking members of the Radiological Devices Advisory Committee, an outside group of experts that provides advice to the FDA regarding radiological devices on an as needed basis, to evaluate the Carestream images. In late February 2010, the review team communicated with representatives from

Carestream and discussed the feasibility of obtaining the actual images from their clinical trial.

In early March 2010, Paul Hardy, the lead reviewer of the Carestream device review team, attended a meeting with OIVD managers, including Donald St. Pierre, Dr. Mary Pastel, and Dr. Michael O'Hara, and was questioned about the Carestream PMA. Mr. Hardy explained that the review team had completed their analysis of the newly submitted post-hoc sub-analysis and that the new submission failed to provide an adequate response to the concerns raised in the April Not Approvable letter. Mr. Hardy further explained that the review team determined that the Carestream PMA failed to establish that the device was safe and effective for detecting cancers that appear as microcalcifications on mammograms and that the team was discussing its options regarding its response. According to the whistleblower, at this meeting, OIVD managers dismissed Mr. Hardy's concerns regarding the detection of microcalcifications and stated that such an issue could be addressed in the labeling of the device after approval. The whistleblower asserted that this was a highly unusual meeting in that OIVD managers did not invite the entire review team to the meeting, only Mr. Hardy, the lead reviewer.

Shortly thereafter, in March 2010, the entire review team again met to discuss the various options regarding the Carestream PMA. According to the whistleblower, this meeting included other experts from inside FDA. At the conclusion of this meeting, the consensus was that a valid methodology could not be devised to evaluate the data previously submitted by Carestream, and that it was not feasible for the FDA itself to conduct additional analyses of the images.

vii. Donald St. Pierre's Alleged Deliberate Circumvention of FDA Review and Approval Process

On April 7, 2010, Mr. Hardy sent a memorandum to Mr. St. Pierre informing him that both his recommendation and that of the review team remained that the Carestream device had not been shown to be safe and effective for the detection and diagnosis of breast cancer and recommending issuance of a second Not Approvable letter. A second Not Approvable Letter would have given Carestream one final opportunity to address FDA concerns regarding the detection of microcalcifications by obtaining additional clinical cases and essentially repeating their clinical study specifically for cancers that appear as microcalcifications on mammograms.

On April 9, 2010, Mr. St. Pierre informed Mr. Hardy by email that he was "not comfortable" with Mr. Hardy's approach and ordered Mr. Hardy to obtain additional consults from Dr. Helen Barr, division director for the Division of Mammography Quality and Radiation Programs, and Dr. Charles Finder, deputy division director serving under Dr. Barr. The whistleblower asserted that this was an extraordinary and unprecedented interference by Mr. St. Pierre, as neither Dr. Finder nor Dr. Barr was a

member of the Carestream device review team, both were members of FDA management in an office separate from ODE, neither Dr. Barr nor Dr. Finder ever served as device reviewers, and it was the role of review team members to obtain additional consults if needed. The whistleblower further asserted that Mr. St. Pierre's actions constituted a deliberate attempt to circumvent FDA regulations governing the approval process. Despite what the whistleblower interpreted as a clear mandate from Mr. St. Pierre to find a way to approve the Carestream device, both Dr. Finder and Dr. Barr recommended that the matter be reviewed by the Radiological Devices Advisory Committee. However, the Advisory Committee was never convened.

On June 9, 2010, Dr. Robert C. Smith, the medical officer on the Carestream review team, prepared an official review memorandum stating that he agreed with Mr. Hardy's recommendation that the FDA issue a second Not Approvable letter. According to the memorandum, Dr. Smith based his finding on Carestream's failure to adequately respond to the deficiency identified in the April Not Approvable letter, as well as on the fact that Carestream had still not established a reasonable assurance of safety and effectiveness for the detection of breast cancers that are revealed on mammography as microcalcifications.

On June 18, 2010, Mr. St. Pierre sent an email to the Carestream review team stating that he had a telephone conversation with representatives from Carestream in which he requested that Carestream submit images from the mammograms of six patients without cancer. The whistleblower asserted that Mr. St. Pierre's actions violated FDA regulations and constituted an attempt by Mr. St. Pierre to circumvent the April Not Approvable letter despite the absence of any appeal or other legitimate reason. The whistleblower further contended that Mr. St. Pierre failed to properly memorialize his actions by placing a review memorandum or other documentation in the administrative file to record and/or explain his actions as required by 21 C.F.R. § 10.70.

On June 21, 2010, Mr. Hardy sent an email to Mr. St. Pierre, reiterating his official recommendation that the FDA issue a second Not Approvable letter. Mr. Hardy further stated that the evaluation of mammograms of six cancer-free patients (*i.e.*, did not contain malignant microcalcifications) could not possibly address the outstanding deficiency regarding whether the Carestream device adequately detected cancers that are revealed on mammograms as microcalcifications.

That same day, Dr. Smith sent an email to Mr. St. Pierre in which he stated that the evaluation of six mammograms, none of which exhibited cancer, had no scientific basis and would not constitute valid scientific evidence in accordance with 21 C.F.R. § 860.7. In this email, Dr. Smith further stated that this is a major public health issue because approximately 40 million women undergo mammography in the United States each year. According to Dr. Smith's email, if the FDA approved the Carestream device, based on the available evidence provided by Carestream to the FDA, "it is likely that

malignant microcalcifications that could have otherwise been detected may be missed." Dr. Smith estimated that approximately 8,000 patients with breast cancer manifesting as microcalcifications on a mammogram could be examined by the Carestream device each year, and that if the Carestream device resulted in the misdiagnosis of even 10% of these cases, the lives and health of nearly 1,000 women per year would affected. "Therefore, even a slightly inferior ability of the Carestream device (compared to, *e.g.*, film screen mammography, the comparator chosen by Carestream) to detect/depict microcalcifications, could have significant Public Health consequences. It is therefore important that the FDA get this issue right."

The whistleblower noted that Mr. St. Pierre did not respond to Mr. Hardy or Dr. Smith. On July 1, 2010, Carestream submitted Amendment A006 for the file that included mammograms of six patients without breast cancer. On July 6, 2010, Dr. Barr sent an email to Mr. St. Pierre, copied to several other managers, but excluding the entire review team including the lead reviewer. Dr. Barr's email stated that on Friday, July 2, 2010, she reviewed the six mammograms obtained using the Carestream device. Dr. Barr's email stated that "for two of the exams the positioning would need to be corrected to make these exams of final interpretive quality, but the quality of these exams other then [*sic*] the positioning, and the quality of the other exams are such that I would feel comfortable interpreting them for screening or diagnostic purposes and feel that, other then [*sic*] the mentioned positioning issues, they are of final interpretive quality." On November 3, 2010, at Mr. St. Pierre's direction, the FDA issued an approval order for the Carestream device.

Following Mr. St. Pierre's decision to approve the Carestream device, Mr. Hardy drafted labeling language for the device which would have required that the manufacturer's label include the actual clinical test results submitted to the FDA by Carestream. These test results, according to the whistleblower, would have revealed to both physicians using the device and the public that the device had serious shortcomings regarding the detection and diagnosis of malignant microcalcifications. Carestream objected to the proposed labeling. Mr. St. Pierre overruled Mr. Hardy with respect to including the actual clinical data on the labeling and threatened Mr. Hardy with disciplinary action if he refused to complete the approval process.

B. The Agency Report

i. OIG Review of Carestream Digital Mammography Device

As with the Viatronix file review, the focus of the OIG's review of the administrative file for the Carestream device was to determine whether documents that reasonably should have been included in the administrative file were present. While the OIG review of the Carestream device file found that it included all letters and emails summarizing the deficiencies in the PMA submission and all other documentation of the

reviewers' analysis, it found that five Review Team Memoranda included in the file were unsigned. The OIG determined that the minutes of nine meetings with the sponsor and four consultations with FDA staff were not included in the file. In addition, the OIG found that the minutes of two additional meetings with the sponsor and one additional consultation with FDA staff, while included in the file, were not signed or dated and that one email between the FDA and the sponsor was referenced but not documented in the file. Finally, an informational letter to the lead investigator at one of the sponsor's clinical investigation sites regarding findings from a data audit of that site was not in the file.

ii. FDA Commissioner Review

The FDA Commissioner reviewed the whistleblower's allegations that the FDA approved Carestream's digital mammography system for use despite review team concerns that the manufacturer failed to empirically refute a trend questioning the effectiveness of the Carestream device in detecting cancers that appear as microcalcifications in the breast. Noting that the issue ultimately revolved around the significance of the conspicuity scores for microcalcifications in the Comparative Features Analysis, the Commissioner found that the Carestream file "documents a lengthy and thorough review in which multiple viewpoints were heard and given a fair hearing" and that clinical reviewers with particular experience in mammography were engaged to clarify concerns raised during the review process. The Commissioner's review determined that the data relied upon by the whistleblower as evidence that the Carestream device was less able to detect malignant calcifications than screen-film was "highly subjective" and "of no clear clinical significance." According to the Commissioner, the available data suggested a preference on the part of the reviewers for screen-film over digital imaging in viewing microcalcifications. It did not, however, indicate that screen-film is better able to detect microcalcifications. Rather, based on the primary study of the safety and effectiveness of the Carestream device, the Commissioner concluded that the sensitivity and specificity of the device was comparable to screen-film. The Commissioner determined that there was no basis for a finding that the use of the Carestream device will lead to significant decreases in the rate at which breast cancers manifested as microcalcifications are diagnosed.

With respect to the whistleblower's allegations of procedural violations related to the review of the Carestream device, the Commissioner found that the deputy director's decision to seek input from experts in mammography, whose function it is to oversee mammography quality standards across the nation, did not violate or appear to violate any law, rule, or regulation. Rather, the Commissioner deemed the deputy director's inclusion of highly qualified mammography experts to assist in the resolution of a long-standing internal debate "reasonable and responsible."

The Commissioner addressed the whistleblower's allegation that the deputy director circumvented the April 9, 2009, Not Approvable letter by requesting that

Carestream submit mammography images from six cancer-free patients to address the microcalcification issue. The Commissioner determined that the deputy director's June 2010 request for additional data was appropriate. In arriving at this conclusion, the Commissioner cited the August 25 informal request for reconsideration meeting between Carestream and the FDA during which, according to the minutes from the meeting, the FDA informed Carestream that, rather than performing a new Comparative Features Analysis, Carestream could submit a reanalysis of existing data. The Commissioner also cited an internal agreement that the deputy director should seek additional images from Carestream. The Commissioner concluded that there are no laws, rules, or regulations precluding the FDA from revisiting or altering a request in a Not Approvable letter.

Finally, the Commissioner addressed the whistleblower's allegation that the deputy director failed to memorialize the June 18, 2010 telephone conversation between the deputy director, the lead reviewer, and Carestream requesting that Carestream submit six additional images with benign examinations. While the Commissioner's review acknowledged that formal minutes documenting the telephone call were not in the file, the administrative file contained a June 18, 2010 email from the deputy director to one of the mammography experts and the review team informing them of the call and referencing the images that were requested from Carestream. The Commissioner concluded that the documentation in the file referencing this call, although not ideal, provided "substantial compliance" with 21 C.F.R. § 10.70 which, as stated above, requires that FDA employees responsible for handling both 510(k) and PMA submissions insure the completeness of the matter's administrative file. Referring to the OIG review of the Carestream device file, the Commissioner noted that the file did not contain formal meeting minutes from several meetings between Carestream and FDA officials, but that these meetings were referenced elsewhere in the file. Similarly, the OIG determined that other meeting minutes which were in the file were not signed and that an email between Carestream and the FDA was mentioned but not included. While the Commissioner concluded that these missing or unsigned documents may have violated § 10.70, these errors were "minor and did not compromise the legal or scientific basis for PMA approval."

The Commissioner's report concluded with a summary of recent CDRH actions taken in response to concerns about the premarket program in general. Since issuance of two reports identifying the need for improvement, CDRH has launched over 35 new initiatives designed to strengthen procedures related to the review of medical devices. According to the report, these actions are designed "to enhance the transparency, predictability, and consistency of the premarket review of medical devices as well as facilitate the appropriate balancing of device benefits and risks." Particularly relevant to the whistleblower's allegations regarding the Carestream device, the CDRH has implemented two new standard operating procedures (SOPs). The first new SOP provides procedures and policies for review staff and managers in compiling the administrative file of agency decisions on premarket submissions to document the facts, data, science, and

deliberative process concerning premarket decisions. The second SOP is intended to resolve internal differences of professional opinion and provides an approach for documenting associated scientific, clinical and regulatory findings, perspectives and opinions. According to the SOP, when differences of professional opinion arise between peers or between an individual and their next-level manager or supervisor that cannot be resolved through discussion, and the parties are unable to align with a decision, then the procedures set forth in this policy can be invoked.

C. Agency Supplemental Report

On March 14, 2014, OSC submitted a request for a supplemental report to Dr. Peter Lurie, the FDA's associate commissioner for policy and planning. OSC's request consisted of 15 follow-up questions. As with the original referral, the agency submitted a bifurcated response to OSC's supplemental report request. A May 7, 2014 response from Mr. Levinson responded to those questions which addressed the scope of the OIG's jurisdiction, whether the OIG properly interpreted and exercised its authority in this matter, and posed factual questions regarding the OIG's review of this matter. A May 13, 2014 memorandum from then-FDA Commissioner Dr. Margaret A. Hamburg to then-Secretary Sebelius responded to the remaining questions regarding the scientific and technical aspects of the review of the Carestream PMA and management of the application's administrative file.

i. Inspector General Response

Mr. Levinson responded to the OSC supplemental questions addressing the scope of OIG jurisdiction and whether the HHS OIG properly interpreted and exercised its authority in this matter. In response to questions regarding the OIG's purported lack of scientific expertise to evaluate the agency decision to approve the Carestream device, Mr. Levinson asserted that the OIG is prohibited by law from exercising "program operating responsibilities" and cannot serve as an avenue to appeal substantive decisions made by program officials. Mr. Levinson acknowledged that the OIG is authorized to conduct reviews of agency decisions to ensure that the decisions followed applicable procedures and were not corrupted by conflicts of interest or misconduct. He asserted that such a review was conducted in this matter.

With respect to OSC's questions regarding the OIG decision to relinquish responsibility for investigating the technical aspects of the whistleblower's allegations, Mr. Levinson asserted that the OIG did not "shy away from" investigating this matter because it involved technical scientific issues. The OIG did, however, decline to draw conclusions concerning the safety or effectiveness of a device or substitute its judgment for that of the agency officials who approved or did not approve the device. Mr. Levinson stated that the OIG "...would not investigate an FDA determination simply because there is professional disagreement in the scientific community concerning the device..."

beyond, perhaps, ensuring that the agency followed established procedures in reaching its decisions.

In response to questions regarding the lack of documentation in the Carestream PMA file memorializing the dispute over and resolution of the approval of the Carestream device, Mr. Levinson cited minutes from the previously discussed July 23, 2012 meeting. During the meeting, the mammography experts presented their views on the efficacy of the device and the lead reviewer modified his non-approvable position and consented to the decision to approve the device. Mr. Levinson attributed the lack of additional documentation in the PMA file regarding the dispute over the approval decision to the fact that the agency's formal dispute resolution processes were never initiated.

Finally, Mr. Levinson responded to a question regarding whether the lead reviewer felt "pressured and bullied" into approving the Carestream device and inquiring whether the lead reviewer was interviewed about this pursuant to the investigation. Mr. Levinson reiterated that the OIG review in this matter was limited to a review of the administrative files and did not include interviews of FDA staff. He did note, however, that in June 2012, the OIG issued a report entitled *Scientific Disagreements Regarding Medical Device Regulatory Decisions* and that the Carestream device review was one of 36 scientific disagreements evaluated in connection with the OIG review. The OIG report in response to the OSC referral was, however, based on document reviews and survey data and did not include staff interviews.

ii. FDA Commissioner Memorandum

At the outset, the Commissioner's memorandum provided general information regarding digital versus film mammography. The memorandum asserted that, while digital and film mammography technologies are similarly effective, traditional mammography devices produce a film image while digital mammography produces a computerized image. Digital images, according to the Commissioner, are advantageous because the images can be enhanced, magnified, and manipulated, thus improving the reader's ability to evaluate and interpret the image. In addition, according to the Commissioner's memorandum, digital images are more easily transmitted, retrieved, and stored. Finally, according to the memorandum, digital mammography exposes patients to potentially lower doses of radiation.

The Commissioner cited a 2005 National Cancer Institute sponsored study concluding that digital mammography was comparable to film mammography with regard to sensitivity and specificity and superior to film for some categories of patients. The study specifically cited women with dense breasts. The use of digital photography in such women is advantageous, according to the study, due to the lack of contrast between cancerous tissue and normal but dense breast tissue. In such cases, the use of digital mammography is preferable because the contrast between the two types of tissue can be

adjusted to enhance visibility. The memorandum further indicated that in November 2010, the FDA acted on two advisory committee recommendations and down-classified digital mammography devices from Class III to Class II. The consequence of this down-classification was that, from that point forward, digital mammography devices were subject to a streamlined application process and a less stringent review. Finally, the memorandum noted that, over the past decade there has been a significant shift towards the use of digital mammography. According to statistics contained in the memorandum, the percentage of mammography units using digital technology increased from 5.5% in 2003 to 93.0% in 2013.

The Commissioner's memorandum revisited the challenges to the Carestream device review raised in the original OSC referral letter. The Commissioner questioned the clinical appropriateness of the whistleblower's reliance on the subjective physician preference for viewing microcalcifications on film given that microcalcifications are only one type of feature and that lesions are typically comprised of mixed features. The Commissioner further noted that the FDA previously approved digital mammography devices with the same study results for sensitivity and specificity as the Carestream device, and that the same trend of a physician preference for film specifically to view microcalcifications had been seen in these other devices. The Commissioner found that alleged defects in the preference data did not provide a sufficient scientific basis for concluding that the approval of the Carestream device would lead to an increase in the misdiagnoses of breast cancers manifested as microcalcifications as compared to traditional film mammography devices.

With respect to the procedural violations alleged in the original disclosure, the Commissioner noted that the use of agency experts outside the review team was permissible and added that, in the case of internal disagreements, consistent with sound review practices. The supplemental report reiterated that there are no laws, rules, or regulations precluding the FDA from modifying a request in a not approvable letter and that the deputy director's request for additional images in this case followed "a sequence of communications" between Carestream and FDA officials attempting to resolve the disagreement regarding subjective preference data relating to microcalcifications. Finally, the supplemental report restated the original report's finding that the Carestream PMA file did not contain minutes from the June 18, 2010 call but did contain an email from the deputy director to the review team and one of the mammography experts. This email informed the recipients of the call and the details of the request made to Carestream for additional images. As in the original report, the Commissioner deemed this email substantially compliant with the requirements of 21 C.F.R. § 10.70, requiring that such communications be memorialized and contained in the file.

The Commissioner responded to the OSC supplemental inquiry regarding the decision to transfer responsibility for assessing the scientific and technical aspects of the original OSC referral to the FDA. According to the Commissioner, then-Secretary

Sebelius made the decision based on notification from OIG that it "does not have the expertise to make this scientific assessment, nor is it authorized to make judgments on agency program decisions." The Secretary made her decision to transfer responsibility to the FDA based on (1) a determination that the FDA was the only HHS component with the expertise needed to address the complex scientific and regulatory issues raised by the allegations, and (2) the Secretary, acknowledging the need for objectivity and independence, asked that the issues not covered by OIG be reviewed exclusively by scientific and regulatory staff in the Office of the Commissioner who were not involved in prior FDA decisions related to the Carestream device or staff from CDRH.

With respect to those questions OSC posed related to the specific findings of the 2012 FDA report, the Commissioner reiterated the agency position that a FDA mammography expert and a statistician were brought in to resolve continuing questions regarding the safety and effectiveness of the Carestream device. The mammography expert evaluated the relevance of the preference analysis that addressed whether reviewers preferred digital images or plain film to view microcalcifications and other features. The mammography expert reviewed the additional images Carestream provided at the agency's request and concluded that the visualizations were of sufficient quality to detect microcalcifications. The minutes from a July 23, 2010 meeting indicated that the mammography expert and statistician explained their conclusion regarding the safety and effectiveness of the Carestream device and that, as a result of this explanation, Mr. Hardy, the lead reviewer, concluded that the issues concerning the preference data had been adequately addressed and ultimately recommended approval of the application. A copy of the minutes from this meeting was provided to OSC.

With respect to the allegation that CDRH did not "satisfy the deficiencies set forth in the Not Approvable Letter" before approving the Carestream application, the Commissioner reiterated the finding earlier in the report that the FDA has the discretion to "revisit or revise" the deficiencies and/or requests articulated in the Not Approvable letter. The Commissioner asserted that there is no law or regulation prohibiting the agency from reconsidering aspects of the letter and there was ample evidence in the PMA file to indicate that the issues raised in the April Not Approvable letter were thoroughly considered and satisfied prior to approval of the device. On this basis, the Commissioner concluded that it was not necessary to include a specific determination that the submission and review of six breast images without malignancies would satisfy deficiencies cited in the not approvable letter.

In response to the inquiry in the OSC supplemental request related to the content of the Carestream PMA file, the Commissioner indicated that the reference in the question to the fact that certain documentation was "not ideal" was mischaracterized. Specifically, rather than referring to the documentation in the PMA file in general, the "not ideal" description referred to one email memorializing a single telephone call between agency officials and Carestream regarding the need for additional images. The

question, according to the Commissioner, further mischaracterized the code section referenced (21 C.F.R. § 10.70) as mandating that the PMA file contain the minutes from any and every PMA-related meeting. Rather, according to the Commissioner, the regulation requires that the file contain "appropriate documentation of the basis for the decision" and affords the FDA discretion in determining which meetings that occur in the course of a medical product review are relevant and significant enough to be included in the PMA file. The Commissioner added that, subsequent to the approval of the Carestream device, the FDA issued a SOP and created a training module regarding the appropriate documentation in a PMA file. Finally, with respect to the documentation issue, the Commissioner asserted that the OIG's review of the file concluded that most of the documents the OIG determined should have been in the file were present and that the absence of certain documents, including minutes from meetings between the FDA and the sponsor and minutes from internal FDA discussions, "provides no legal basis for invalidating the Agency's approval [of the Carestream device], which was based on objective, scientific evidence."

In response to the OSC supplemental questions requesting additional documentation, the Commissioner produced some information from the PMA file. The documentation that was not produced, according to the Commissioner, contained confidential commercial information and/or trade secrets. With respect to those questions in the OSC supplemental request inquiring as to the actions and beliefs of review team participants during the course of the Carestream PMA review, the Commissioner indicated that descriptions and explanations of events and motivations were not specifically documented in the PMA file. According to the Commissioner, the scientific or procedural allegations originally referred to the Secretary did not raise issues that could be resolved through the testimony of the participants and, therefore, testimony was not taken during the course of the investigation. Rather, the question of whether there was an adequate scientific basis for finding that the Carestream device was safe and effective was evaluated based on the content of the PMA file. Similarly, the question of whether any procedural violations occurred could be resolved by reference to the evidence in the file. It was, according to the Commissioner, unnecessary to go beyond the file itself.

The majority of the remaining supplemental questions OSC submitted to the agency requested clarification on various communication among agency officials and/or between agency officials and Carestream representatives. The final responses the Commissioner provided related to allegations that members of the review team were coerced or pressured into approving the Carestream PMA application. In response to the OSC request that the agency provide testimony from members of the review team on this issue, the Commissioner asserted that testimony cannot be taken at this point because of lawsuits filed by some of the reviewers against the FDA. These lawsuits, according to the Commissioner, contain allegations of coercion. Nevertheless, the Commissioner further cited the fact that there is no documentary evidence to support the reviewers' accusations of coercion. Noting that the PMA file includes records documenting the "scientific views

and disagreements" among the reviewers or between the reviewers and management, the Commissioner asserted that there is no documented allegation or suggestion of coercion. The Commissioner further asserted that there was a process in place for the handling of disagreements between reviewers and managers and that none of the reviewers involved in the Carestream PMA initiated this process either during the course of the review or following the approval decision.

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I have reviewed the original disclosure, the agency's reports, and its answers to OSC's supplemental questions. I have determined that the reports meet all statutory requirements and that the findings of the agency head appear reasonable. I commend the agency for taking positive steps to make the medical device premarket approval process more transparent, predictable, and consistent. These efforts, according to the report, include more than 35 new initiatives designed to strengthen the review procedures. In addition, the new CDRH SOPs will govern the compilation of the administrative file to ensure adequate documentation of the facts, data, science, and deliberative process concerning premarket decisions and will facilitate the appropriate balance of device benefits versus risks. A second CDRH SOP addresses internal differences of professional opinion and dictates an approach for documenting associated scientific, clinical and regulatory findings, perspectives and opinions. By continuing to encourage respectful scientific debate, the agency will help ensure that medical devices approved for public use are as safe and effective as possible.

As required by 5 U.S.C. § 1213(e)(3), I have sent copies of the agency's reports to the Chairs and Ranking Members of the Senate Committee on Health, Education, Labor & Pensions and the House Committee on Energy & Commerce. I have also filed copies of the reports in our public file, which is now available online at www.osc.gov, and closed the matter.

Respectfully,

Carolyn N. Lerner

Enclosures