THE SECRETARY OF HEALTH AND HUMAN SERVICES
WASHINGTON, D.C. 20201

May 14, 2014

The Honorable Carolyn Lerner
Special Counsel
U.S. Office of Special Counsel
1730 M Street, N.W. Suite 300
Washington, D.C. 20036-4505

Dear Ms. Lerner:

On May 31, 2012, you sent me a letter (OSC File No. DI-11-3325) containing various allegations, under 5 U.S.C. § 1213, concerning the review by the Food and Drug Administration (FDA) of certain applications for premarket review or clearance of specific medical devices. On October 1, 2012, I transmitted to you the detailed reports compiled by the Commissioner of Food and Drugs and the Inspector General of the Department of Health and Human Services (HHS) in response to your referral.

On March 14, 2014, Catherine McMullen of your staff sent an e-mail to FDA staff with numerous additional questions relating to FDA's review of the Carestream digital mammography device, which is one of the two medical devices that were the subject of your May 31, 2012, letter. The Inspector General, by letter to you dated May 7, 2014, has separately answered those questions that pertain to his office, and I have provided FDA with information responding to a question regarding my assignment of the May 31, 2012, referral to the Commissioner of Food and Drugs.

Enclosed is a detailed Supplemental Report provided by the Commissioner of Food and Drugs that addresses the additional questions provided by your office. As with the October 1, 2012, report, this Supplemental Report was conducted by scientific and regulatory staff in FDA's Office of the Commissioner, who were not involved in prior FDA decisions on the devices in question.

Sincerely,

Kathleen Sebelius

Kathleen Sebelius

Enclosures

DEPARTMENT OF HEALTH AND HUMAN SERVICES

OFFICE OF INSPECTOR GENERAL

WASHINGTON, DC 20201

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U.S. OFFICE OF SPECIAL COUNSEL WASHINGTON, DC

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The Honorable Carolyn Lerner
Special Counsel
U.S. Office of Special Counsel
1730 M Street, N.W. Suite 300
Washington, D.C. 20036-4505

Dear Ms. Lerner:

In June 2012, you forwarded to the Secretary of Health and Human Services (HHS), Kathleen Sebelius, a whistleblower disclosure alleging improper conduct by employees of the Food and Drug Administration (FDA). In accordance with 5 U.S.C. § 1213, you requested that the Secretary investigate FDA's review of certain applications for premarket approval or clearance of specific medical devices and report back to you. Initially, the Secretary asked that the HHS Office of Inspector General (OIG) investigate. Our attorneys assessed the allegations and concluded that some exceeded the jurisdiction of the OIG. We so advised the Secretary by interim response dated July 25, 2012, and proceeded to conduct a review of those matters that were within our authority. Secretary Sebelius then asked the Commissioner of Food and Drugs to investigate the regulatory matters posed by your letter that exceeded our authority. The inquiries by both FDA and OIG were completed; after a brief extension (granted by your office), on October 1, 2012, the Secretary transmitted to you the reports of both offices.

On March 28, 2014, we learned that your staff had emailed Dr. Peter Lurie, Associate Commissioner for Policy and Planning at FDA, posing 15 follow-up questions to the 2012 reports. Four of these questions addressed the scope of OIG jurisdiction and whether we had properly interpreted and exercised our authorities in this matter, or posed factual questions about our review.

By law, statutory Inspectors General are subject to supervision only by the head of their agency and not by subordinate agency officials.[1] Even the Secretary may not "prevent or prohibit the IG from initiating, carrying out, or completing any audit or investigation." Thus, since the decisions challenged in the follow-up email from your office were made solely by the OIG, these four questions have been forwarded to my office for response.

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[1] The Act states that that each IG "shall report to and be under the general supervision of the head of the establishment involved or, to the extent such authority is delegated, the officer next in rank, but shall not report to, or be subject to supervision by, any other officer of such establishment." (IG Act, § 3(a), 42 U.S.C. App. 3, § 3(a)).

Below, we have restated, verbatim, the incoming questions from your office that pertain to OIG authorities and actions and we have replied to each.

Question 1: ***"With regard to the agency position that the HHS OIG does not have the "scientific expertise" to evaluate the agency decision to approve the Carestream device, please explain how the HHS OIG effectively functions and meets its statutory mandate without a staff that includes personnel capable of evaluating underlying scientific and medical issues."***

We included an Appendix to our interim response dated July 25, 2012 that set out the legal basis for our interpretation of OIG jurisdiction. For ease of reference, we are enclosing that Appendix to this letter, as well. Briefly, the OIG is prohibited by law from exercising "program operating responsibilities." Congress was concerned that if an IG played a decision-making role in a regulatory or management action, then the IG could no longer objectively audit, investigate, or evaluate that action. Thus, the OIG does not and cannot serve as an avenue to appeal the substantive decision of program officials of any of the 300 diverse programs administered by HHS, including FDA. As set out in detail in the enclosed Appendix, Congress specifically stated that IGs were not intended to question the scientific merits of a specific grant proposal or render judgment on the agency's exercise of discretion in a particular proceeding. For this reason, we declined to render judgment concerning the assessment of the safety of the devices identified in your referral to the Secretary. We continue to believe that this was the appropriate legal reading of the IG Act.

While we do not substitute our judgment for agency decision-makers, the OIG is fully authorized to conduct reviews to ensure that agency decisions followed applicable procedures and were not corrupted by conflicts of interest or misconduct. We did such a review here. Specifically, we conducted a file review to determine whether FDA appropriately documented significant decisions associated with clearance of the identified devices as required by agency regulation.

Because the OIG cannot and does not assume the role of agency program officials, the OIG does not duplicate the medical, scientific and technical expertise of the many thousands of employees across HHS. Instead, as envisioned by the IG Act, we employ auditors, investigators, program evaluators, and attorneys.

Question 3: ***"Was consideration given to having the OIG retain consultants or outside expert assistance to address the technical aspects of the allegations in order to minimize the possibility or appearance of partiality? The whistleblower contends that OIG previously conducted investigations as a result of prior disclosures regarding alleged abuses during the regulatory review of the GE CT Colonography device. These previous investigative reports, according to the whistleblower, contained highly technical medical and scientific concepts and language. Why, in the current matter, did OIG relinquish responsibility for investigating the technical aspects given that it apparently was/is "qualified" to make scientific assessments in previous matters?"***

First, as drafted, the question seems to ask whether FDA gave consideration to having the OIG engage expert consultants for the instant review. As mentioned above, the IG reports to and is supervised only by the Secretary. Accordingly, FDA officials could not compel the OIG to engage an expert consultant.

The IG Act does authorize the OIG to "enter into contracts and other arrangements for audits, studies, analyses and other services." (IG Act, § 6(a)(9)). Under this authority, we often engage experts to assist in ongoing investigations, audits or evaluations that are within our jurisdiction. For example, we frequently contract with medical experts who opine on whether health care items or services provided to a Medicare beneficiary were "reasonable and necessary for the diagnosis or treatment of illness or injury," as is required by law. Where the provider's care was found to be medically unnecessary, we recommend to the program agency that it recover payment for those services. In egregious cases, we pursue civil or criminal false claims cases.

In contrast, we know of no instance in which the OIG has, under its contracting authority or otherwise, rendered judgment on the discretionary decision made by an authorized HHS official (e.g., selection of a contractor or grantee; approval of a medical device or new drug). Again, we do not have authority to make or reverse those determinations that are vested in agency management and so would not engage an expert to do so.

The OIG does not shy away from inquiries or reviews simply because they involve technical scientific issues. As the Inspector General for a department that runs hundreds of health and social services programs, we encounter complex medical issues daily. What we decline to do is to make conclusions concerning the safety or effectiveness of a particular device or substitute our judgment for the decision to approve or not approve that device. To be clear; it is entirely legal and appropriate for authorized FDA officials to weigh the relative merits of an application and exercise discretion to approve or not approve a particular device. The OIG would not investigate an FDA determination simply because there is professional disagreement in the scientific community concerning the device. The OIG could inquire to ensure that the agency followed established procedures in reaching those decisions; but we may not commandeer the FDA's authority to make the decision and we may not reverse the decision once made.

Question 11: ***"Page 7 of the OIG interim report references a June 23, 2010, review team meeting at which the lead reviewer changed his recommendation to issue a second Not Approvable letter to approve the Carestream device. According to the report, the "disagreement [over whether to approve the device] appears to have been resolved at that meeting," however, there was no documentation in the file addressing the disagreement and its resolution. If the June 23 meeting was not documented, how did the OIG review team arrive at the conclusion that the disagreement was resolved at that meeting and how it was resolved?"***

The OIG's interim response to the Secretary dated July 25, 2012, described a review team meeting held on July 23, 2010. (Our interim response mistakenly described that meeting as having occurred on June 23, 2010.) The minutes of that July 23, 2010 meeting were in the file and included a description of how the disagreement was resolved. The FDA Review of

Whistleblower Allegations, dated October 1, 2012 and submitted to your office, includes on page 26 the following description of those minutes:

> On July 23, 2010, a meeting including the Deputy Director, the lead reviewer, and the two mammography experts took place. Initially, the lead reviewer indicated that the application was non-approvable, based on the trend in the CFA toward a preference for screen-film for detecting microcalcifications. The Deputy Director indicated that the statistician and the mammography experts had concluded that the device was safe and effective, differing from the lead reviewer's recommendations. According to the meeting minutes, after the statistician and expert mammographers stated their views, the lead reviewer "said that there are new issues that the discussion brought to light … he now feels comfortable with the microcalcification issue."

This description accurately reflects the minutes of the July 23, 2010 meeting.

In the OIG interim response, we stated that no document formally addressed the disagreement and its resolution. As stated in our response, the reason no such formal dispute resolution document was in the file is that no party formally initiated the dispute resolution process.

Question 15: ***"According to the whistleblower, the Lead Reviewer felt "pressured and bullied" into recommending that the device be found safe and effective at a July 23rd meeting. Are minutes from this meeting contained in the administrative file? If so, please provide a copy of these minutes. Was the Lead Reviewer interviewed pursuant to either the OIG investigation or the FDA investigation? If not, why? If so, please provide a copy of his testimony regarding his version of the July 23rd meeting specifically and, generally, his opinion regarding the review and approval process for the Carestream device."***

We are responding to the portion of this question that pertains to decisions and actions by the OIG. In response to the June 2012 referral from your office to Secretary Sebelius, the OIG undertook an evaluation of the completeness of the administrative files for particular devices identified by the OSC whistleblower. Our review was based on a review of information in the administrative files; we conducted no interviews of FDA staff during the course of the evaluation.

Earlier, in June 2012, OIG issued a report entitled *Scientific Disagreements Regarding Medical Device Regulatory Decisions* (OEI-01-10-00470) (http://oig.hhs.gov/oei/reports/oei-01-10-00470.pdf). This report looked at the handling of 36 scientific disagreements in connection with device applications reviewed by FDA's Center for Devices and Radiological Health (CDRH). The Carestream device was among the 36 files. This OIG evaluation was based on documentary reviews and survey data; we did not interview staff of the FDA.

Finally, the OIG did investigate various allegations of misconduct lodged against managers within CDRH. Interviews were conducted during those investigations; however, these interviews predated the July 23, 2010 meeting. Thus, these interviews could not have addressed the issue of whether the reviewer felt unduly pressured during that meeting.

We hope that you find the above information helpful. If you have questions or would like additional information concerning reports of the OIG, please contact our office directly; you may contact me or our Chief Counsel, Gregory Demske. Mr. Demske may be reached at gregory.demske@oig.hhs.gov.

Sincerely

Daniel R. Levinson
Inspector General

Enclosure

Attachment: Office of Inspector General Jurisdictional Limitations

Under the Inspector General Act (5 U.S.C. App. 3), each Office of Inspector General (OIG) is charged with protecting the integrity of programs funded or administered by its parent agency, by undertaking investigations, audits, and evaluations of fraud, abuse, misconduct, and mismanagement in connection with those programs. There are, however, legal limitations on OIG authority. The Inspector General Act generally prohibits this office from assuming day-to-day "program operating responsibilities." (5 U.S.C. App, 3 § 9). In this way, OIG remains objective and independent when it is called upon to audit, investigate, or otherwise review Department of Health and Human Services (HHS) programs.

The legislative history that accompanied the passage of the Inspector General Act best illustrates the limitations that Congress imposed on the programmatic responsibility of the Inspectors General.

> The Inspector General Act authorizes each such IG to promote economy and efficiency in the administration of, and prevent and detect fraud and abuse in, programs and operations of the designated Federal entities. The IGs are intended to act as independent fact-gatherers, with no vested interest in policy, or in particular programs and operations. For example, the conferees do not intend that the IG at the National Science Foundation question the scientific merits of a specific grant or contract proposal or that the IG at the FEC render judgment on the Commission's exercise of discretion in a particular cause or controversy involving enforcement of or compliance with the campaign finance laws. (House Conference Report No. 100-1020, p. 28.)

And further:

> Broad as it is, the [Inspector General's] mandate is not unlimited. Issues requiring substantive or technical expertise will often fall outside his proper sphere. For instance, if the [Inspector General] at the Environmental Protection Agency received a report that a new type of sewage treatment system in Milwaukee was not functioning according to specifications, resulting in dangerous levels of pollution, the [Inspector General] could quite properly decide that responsibility for handling the issue rested elsewhere and make the proper referral. (Senate Report No. 95-1071, p. 28.)

In short, OIG may not substitute its judgment and overrule discretionary decisions made by agency officials with responsibility for HHS programs. OIG may ensure that agency procedures are duly followed and are not corrupted by self-dealing or misconduct.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

May 13, 2014

TO: Kathleen Sebelius
Secretary

FROM: Margaret A. Hamburg, M.D.
Commissioner of Food and Drugs

SUBJECT: Supplemental Report to the U.S. Office of Special Counsel (OSC File No. DI-11-3325)

This Supplemental Report responds to new questions from the Office of Special Counsel (OSC) sent on March 14, 2014. On May 31, 2012, OSC referred to HHS various allegations about the safety and approval of certain medical devices. The Food and Drug Administration (FDA) and the Office of the Inspector General (OIG) provided separate reports to you on aspects of the referral letter, and HHS responded formally to OSC on October 1, 2012. (Attachment A.) The new questions were contained in an email dated March 14, 2014, from Catherine McMullen, Chief, Disclosure Unit, OSC, to Peter Lurie, M.D., Associate Commissioner for Policy and Planning, FDA. OSC's questions concern FDA's review of one of the two devices described in the original referral letter, the Carestream digital mammography device. In the body of the Supplemental Report, we first summarize the findings in the 2012 FDA report with respect to the Carestream device, and then we address the new questions concerning the procedural history of FDA's review of that device.

I. Background

A. Original Referral Letter

OSC's referral letter of May 31, 2012 contained the following allegations:

1. *FDA reviewers used the agency's 510(k) review process to assess CT colonography devices that required a more stringent level of review prior to clearance;*

2. *The improper clearance of the devices led to their use on asymptomatic patients, potentially exposing millions of otherwise healthy people to unnecessary radiation and creating a significant increased cancer risk; and*

3. *FDA reviewers approved a specific digital mammography system for use despite the fact that the manufacturer failed to provide adequate clinical data to support the safety and effectiveness of the system after its original application was found deficient.*

FDA's report to you of October 1, 2012 (2012 FDA report) made the following findings:

1. In response to the first allegation, the 2012 FDA report concluded that FDA reviewers properly used the 510(k) process to assess CT colonography devices for asymptomatic screening. The report found that the decisions of the Center for Devices and Radiological Health (CDRH) related to the intended use of these devices were consistent with the statute and regulations. The report also found, on the basis of the OIG review, a small number of documentation errors, but these did not call into question the legal or scientific basis of the 510(k) in question.

2. In response to the second allegation, the 2012 FDA report found that the CDRH's conclusion that the benefits of CT colonography outweigh its risks was based on a thorough and appropriate evaluation of the risks and benefits of CT colonography for screening of asymptomatic patients. An appropriate benefit-risk assessment is complex and requires an assessment of comparable alternatives and unmet medical needs as well the specific risks and benefits of the device standing alone. Here, colorectal cancer is the second leading cause of cancer deaths in the U.S. and colorectal screening of all adults over 50 years old could cut the number of colorectal cancer deaths in the U.S. by more than half. Yet screening rates remain relatively low, in part because many patients are reluctant to undergo colonoscopy. Having available other safe and effective screening options is therefore an important public health goal. To carry out its evaluation, CDRH appropriately reviewed the advantages and disadvantages of both CT colonography and colonoscopy, including the risks associated with each method, the number of cancers that could be prevented with universal screening, the currently low rates of screening with colonoscopy, and the likelihood that having CT colonography available as an option will increase the number of Americans who undergo screening.

The 2012 FDA report also found no significant basis for the complainant's allegation that the use of CT colonography for asymptomatic screening is likely to result in an increase of 7,000 cases of colon cancer per year, or that the risk of CT colonography outweigh the benefits. The complainant did not state his or her assumptions or provide scientific evidence to support this assertion. It is unlikely that the estimate takes into account the number of colon cancers that would be prevented by the early detection of pre-cancerous polyps through CT colonography, or other factors associated with an adequate risk-benefit analysis. To FDA's knowledge, none of the outside scientists or groups who had studied or reviewed CT colonography, including those who had expressed concern about the radiation risk, had suggested that the technology would result in a net increase in the number of colon (or other) cancers. A recent, well-designed risk-benefit analysis co-authored by a scientist who frequently warns of the risk of radiation exposure from medical devices directly compared the risks of radiation-induced cancers against the benefits of preventing cancers using CT colonography, and found that CT colonography would prevent 24-35 times as many cancers as it could induce.[1]

In light of evolving information on the risks and benefits of CT colonography devices for screening asymptomatic patients, FDA held a public meeting of two of its advisory committees,

[1] Berrington de Gonzalez A, Kim KP, Knudsen AB, et al. Radiation-Related Cancer Risks from CT Colonography Screening: A Risk-Benefit Analysis, Amer J of Roentgenology, 2011;196:816-823; available online at http://www.ajronline.org/content/196/4/816.long.

whose members are independent, outside experts on radiology and gastroenterology, on September 9, 2013. Weighing the most current information on the benefits and risks of CT colonography, the advisory committee members unanimously concluded that CT colonography should be available as an option for colorectal cancer screening.

3. In response to the third allegation, which focused on the Carestream digital mammography device, the 2012 FDA report concluded that the device was appropriately found to be safe and effective on the basis of valid scientific evidence. The specific study result about which the complainant had concerns did not undermine the overall finding of safety and effectiveness. The report also found that procedures followed in the review of the device did not violate or appear to violate any laws, regulations, or rules, and that the small number of documentation errors did not call into question the legal or scientific basis of the PMA approval. The report concluded that these allegations did not raise any issues warranting review by an advisory committee.

OSC's March 14, 2014, email sets out a number of new questions concerning the procedural history of the original Carestream PMA review. It does not raise any additional questions about FDA's review of CT colonography devices. None of the new questions allege any new violations of applicable laws or rules or raise any new scientific issues.

B. FDA Review of Digital Mammography Devices

Digital mammography devices are very similar to traditional mammography devices. Both types of devices use x-rays to visualize abnormalities in breast tissue and help detect cancer. The difference between the two technologies is simply that a traditional mammography device produces film images, while digital mammography produces computerized images. Digital images provide capabilities that are not available with film, including ability to enhance, magnify, or manipulate images for further evaluation as well as improved means of transmitting, retrieving, and storing images. In addition, digital systems offer the potential for lower doses of radiation with similar image quality. Digital technology is rapidly replacing film in all types of radiological imaging.

In determining whether a digital mammography device is as safe and effective at detecting cancer as a screen-film mammography device, the definitive test is whether the images produced by the two types of devices are comparable in sensitivity (how often will the test correctly detect a known cancer) and specificity (how often will the test correctly conclude that cancer is not present).[2]

In 2005, a major trial, known as the Digital Mammography Imaging Screening Trial (DMIST) study, which was sponsored by the National Cancer Institute (NCI) and was one of the largest breast cancer screening studies ever performed, concluded that digital mammography was not only comparable to screen film mammography in sensitivity and specificity, but superior for

[2] Skaane P. Studies Comparing Screen-Film Mammography and full-Field Digital Mammography in Breast Cancer Screening: Updated Review, Acta Radiologica 2009;50:3-14.

some categories of patients.[3] In particular, digital mammography was superior in detecting cancers, including serious cancers, in women with dense breasts. These women are at higher risk for breast cancer, but traditional film images make it difficult to detect their cancers because there is so little visible contrast between the cancerous tissue and the normal but dense tissue. With digital images, the contrast can be adjusted to increase the visibility of abnormal tissue. The NCI study results were derived using digital mammography devices that use both types of available digital imaging systems: digital radiography (DR) and computed radiography (CR).

Responding to the NCI-sponsored study, an advisory committee of outside experts on radiological devices twice unanimously recommended, in 2006 and 2009, that FDA reclassify digital mammography devices from Class III to Class II and dispense with the requirement that each new device obtain approval of a PMA. In other words, the outside experts advised that FDA's data and review standards (Class III review) were unnecessarily stringent in view of the well-accepted evidence supporting safety and effectiveness of digital mammography devices. These experts concluded that digital mammography devices should be "down-classified" to a less stringent review path (Class II review) that can be cleared through a streamlined application known as a 510(k).

Before 2006, FDA had approved premarket approval applications (PMAs) (Class III) for five digital mammography devices, including those with DR and CR systems.[4] A PMA for the Carestream Kodak DirectView Computed Radiography Mammography System (the Carestream device) was first submitted in 2005 and resubmitted in 2008. Between 2006 and 2010, no PMAs for digital mammography devices were approved.
FDA acted on the advisory committee recommendations and down-classified digital mammography devices in November 2010. The Carestream PMA, also approved in November 2010, was the sixth and last PMA to be approved before the down-classification. FDA has subsequently cleared over a dozen 510(k)s for digital mammography devices.

The past decade has seen a remarkable shift from non-digital mammography to digital mammography. According to national statistics compiled by FDA's Mammography Quality Standards Act program, the percentage of mammography units using digital technology has increased from 5.5% in 2003 to 93.0% in 2013. CR units, a subset of digital units, first came on the market in 2006 and have accounted for an increasing percentage of mammography units over time, reaching 10.9% in 2013.

II. FDA's 2012 review of the Carestream allegations in the original referral letter

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[3]Pisano ED, Gatsonis C, Hendrick E, et al. Diagnostic Performance of Digital versus Film Mammography for Breast-Cancer Screening, N Engl J Med 2005;353, http://www.acrin.org/Portals/0/Protocols/6652/Publications/NEJMoa052911v1%20(2).pdf; NCI/NIH, Digital Mammography Trial Results Announced: Women with Dense Breasts, Women Younger than 50, and Those Who are Perimenopausal May Benefit from Digital Mammograms, http://www.cancer.gov/newscenter/newsfromnci/2005/dmistrelease.

[4] FDA classifies devices with either DR or CR systems as Full-Field Digital Mammography (FFDM) devices. 21 CFR § 892.1715.

A. Scientific issues

According to the 2012 original referral letter, the complainant alleged that FDA reviewers approved the Carestream digital mammography device for use "despite the fact that the manufacturer failed to provide adequate clinical data to support the safety and effectiveness of the system after its original application was found deficient."

The letter also stated that use of the device in breast cancer screening "may, according to the complainant, lead to a significant increase in the misdiagnoses or undiagnoses of breast cancers manifested as microcalcifications."

To provide an objective, independent review of the allegations in the original referral letter, FDA's review was carried out by medical and legal staff in the Office of the Commissioner (OC) who had no prior role in FDA's review of the devices in question. Staff from CDRH did not participate substantively in the review. The OC staff carefully reviewed the entire PMA file, including all submitted data and information, as well as internal FDA documents contained in the file.

Based on this independent investigation, FDA's 2012 report to the Secretary found that the safety and effectiveness of the Carestream digital mammography device was established with compelling, objective scientific evidence and that the approval was appropriate. In particular, the report concluded that the pivotal multi-center clinical study in the PMA, which compared the sensitivity and specificity of the Carestream device to screen-film mammography, established that the Carestream device was comparable to screen-film in its ability to accurately diagnose breast cancer.

Indeed, the allegations in the referral letter did not challenge the results of the objective, scientific data showing the comparable sensitivity and specificity of the images produced by the Carestream device and traditional screen-film. Instead, the allegations focused on a secondary, more subjective analysis of whether eight physicians who subsequently reviewed the images in the primary study preferred one type of image over another, when looking at a range of different features of the images. The complainant's claims all depended on his assertion that for only one of several types of findings there was a trend toward a minimal to mild preference for film.[5] Overall, there was no difference in the preferences for screen film or the Carestream images.

Contrary to a statement in the referral letter, this was not an analysis of whether the Carestream device could "reveal cancers as well as film." It was an analysis of whether eight physicians,

[5] According to a review by a medical reviewer, the results of the preference data on microcalcifications showed that on a scale of -4 (strong preference for screen film) to +4 (strong preference for), where 0 = no preference, the physicians in the study gave the images an average score of -0.4 to -0.8 (between no preference and screen film "minimally" better), with a 95% lower confidence bound of -0.9 to -1.5 (screen film "minimally" to "mildly" better). The medical reviewer referred to these results as revealing a "strong" trend toward screen film, while the statistician and expert mammographers concluded that these results amounted to a "slight trend." The reviewers in the Office of the Commissioner concurred that these data showed no more than a slight trend in favor of a preference for screen film, and even then on only one of the nine features being rated. On the remaining features, the physicians showed no preference or preferred the Carestream images.

looking at the same images whose readings had already demonstrated that Carestream and film images were comparable in their ability to accurately diagnose breast cancers, subjectively preferred looking at the digital or film images in particular respects. The preference data were intended to provide secondary, "descriptive," not statistical, information on physicians' subjective views of the overall "conspicuity" of lesions seen in the images; those data were not intended to measure ability to detect cancer. The issue of comparative ability to accurately diagnose cancer is objectively addressed by the sensitivity and specificity analysis conducted in the primary study in which the CR had already met its prespecified goals.

For 18 months after the PMA was submitted, at the behest of certain FDA reviewers, FDA issued a series of letters to the sponsor, including a Major Deficiency letter and a Not Approvable letter, seeking additional information and reanalyses of the preference data. None of the sponsor's submissions in response were deemed adequate by these reviewers. In 2010, the Deputy Division Director brought in two FDA mammography experts to clarify the relevance of the concerns about the preference data. Before that time, there were no mammography experts on the review team. FDA's mammography experts concluded that subjective physician preferences were not clinically important in this context.

The complainant focuses on the preference for only one of several features measured in the preference study, microcalcifications. (For the remaining features, the two technologies were either similar or there was a preference favoring the Carestream images.) According to the senior mammography expert, in explaining why it was not clinically appropriate to pick out physician preferences on a single type of feature, "mammographic lesions indicating cancer are not purely of one type—that is not solely masses, architectural distortion, microcalcification, but are mixed. Therefore . . . overall lesion conspicuity [one of the nine features measured]. . . is the most important component." Here the preference data showed the Carestream images were comparable to screen film on overall conspicuity.

The mammography experts also concluded that the study results for sensitivity and specificity of the Carestream device were not different from those of previously approved digital mammography devices. Moreover, the same trend of minimal to mild preference for screen-film to view microcalcifications had also been seen in other approved digital mammography systems. (In fact, some previous digital mammography devices had not even been required to carry out a preference analysis comparing digital and screen film images.)

Both experts noted that FDA had no apparent review standards for evaluating the preference data, and the senior mammography expert questioned what scientific and regulatory basis the reviewers had for attempting to use subjective preference data as an objective measure of device safety and effectiveness. She concluded: "As an experienced mammographer, I would accept a preference in this range, given the wide range of reader variability, and I would not think that such a preference meant that there isn't a reasonable assurance of safety and effectiveness." She also observed that, even though the slight trend for microcalcifications has been seen for other digital mammography devices, clinical experience both in the US and abroad with digital mammography, as well as the results of the DMIST trial, have not revealed evidence that cancers found in microcalcifications are being missed.

During this period, an advisory committee of outside experts on radiological devices also met, recommended down-classification of digital mammography for the second time, and did not include the preference analysis among the studies recommended for applications for digital mammography devices. (As a result, such preference studies are no longer required for clearance of these devices.)

These developments alone could have justified CDRH supervisors in ending the debate on the preference data and approving the PMA. Nevertheless, in June 2010, CDRH supervisors agreed to have the sponsor submit additional images of microcalcifications from the Carestream device to assess their conspicuity. When the images were submitted, however, two of the reviewers said that the images were inadequate because they did not include patients with cancer. The senior mammography expert reviewed the images and determined that: (1) they were adequate to establish the ability of the device to visualize microcalcifications; and (2) it was not relevant, for these purposes, whether the microcalcifications were benign or malignant because the conspicuity of a microcalcification was not dependent on whether the lesion within which the microcalcification was contained was benign or malignant. She concluded that the images of microcalcifications from the Carestream device were of "final interpretive quality," i.e., of high enough quality for use in issuing final mammography reports.

On July 23, 2010, at a meeting that included Mr. St. Pierre, the Acting Director of the Division, Mr. Paul Hardy, the Lead Reviewer, Dr. Gwise, the statistician, and Drs. Barr and Finder, the two mammography experts, the Lead Reviewer at first indicated that he felt that the application was not approvable because of the trend in the physician preference data. According to the meeting minutes, however, the mammography experts and the statistician explained why they believed that the device was safe and effective. The senior mammography expert said that the trend in the preference data was not clinically important, and that the preference data on the Carestream device was actually better than the preference data on another already approved digital mammography device. The Acting Division Director expressed concern that the Lead Reviewer's basis for recommending against approval "was a clinical and statistical issue," and yet "the clinical expert and the statistician were both recommending approval." The Lead Reviewer then "said that there are new issues that the discussion brought to light," that the microcalcification issue had been adequately addressed, and that he would recommend that the application be approved. The Lead Reviewer issued an "approvable" recommendation, and the Carestream device was approved in November 2010. The Lead Reviewer did not initiate an appeal of this or any earlier decision or pursue the formal process established to resolve scientific disagreements.

The 2012 FDA report concluded that the original decision to approve the Carestream PMA was medically and scientifically appropriate. The report concluded that a mild trend in subjective physician preferences for screen-film in one of nine of the secondary analyses could not undercut the more robust primary, objective scientific finding that the Carestream device was comparable to film mammography in its ability to accurately diagnose cancers. The FDA review concluded that it was not necessary to have obtained the additional information about the preference data that the complainant sought, because it could not have altered the conclusion that the safety and effectiveness of the Carestream device had been reliably demonstrated. Finally, the report concluded that, for the same reasons, any defects in the preference analysis did not provide a

scientific reason to believe that approval of the Carestream device would lead to a significant increase in the misdiagnoses of, or failure to diagnose, breast cancers manifested as microcalcifications, compared to traditional mammography devices.

B. Procedural issues

1. Procedural history of the Carestream PMA

As described in the 2012 FDA report, the Carestream PMA file reveals that some of the FDA reviewers were repeatedly unsatisfied with the information submitted by Carestream. FDA supervisors consistently permitted these reviewers to request additional data to address their concerns, and issued a series of Not Approvable and Major Deficiency letters from the original submission of the PMA in 2006 through its resubmission in 2008 and throughout 2009 and much of 2010. Beginning with the resubmission of the PMA, the additional information sought by the reviewers was predominantly about the subjective "preference" analysis, described in section I. The objecting reviewers did, initially, have some questions about the primary study establishing the comparable sensitivity and specificity of the Carestream device to traditional film mammography, but these questions were resolved early in the review. Their supervisors permitted those reviewers to seek more information and explore their concerns about the subjective preference data for almost two years. The PMA was approved only after supervisors sought to resolve the long-standing scientific issues concerning the subjective preference analysis by obtaining the specialized review of the FDA mammography experts. The mammography experts concluded that the additional subjective preference data that the Lead Reviewer felt should be required before approval were in fact scientifically unnecessary for a determination of safety and effectiveness, and the Lead Reviewer ultimately agreed that the safety and effectiveness of the Carestream device had been adequately demonstrated.

It is not uncommon for there to be internal scientific and regulatory disagreements in the course of medical product reviews. An administrative agency must be able to resolve those disagreements in a fair yet timely manner. FDA, in particular, has dual responsibilities: to appropriately evaluate the safety and effectiveness of particular devices, and to provide an efficient and timely review that gives Americans access to safe and effective new technologies as soon as possible. To satisfy the first of these responsibilities, the process for resolution of such disagreements strives to ensure that all viewpoints are given a full and fair hearing. CDRH's procedures for resolving scientific disagreements emphasize that efforts should be made to resolve disagreements informally, but also provide a formal disagreement resolution process if informal discussions do not resolve the issue.[6]

To satisfy the second of these responsibilities, FDA has a duty to ensure that a statutorily mandated product review is not unreasonably delayed, e.g., by demands for unnecessary information, and does not unjustifiably consume limited agency resources. Although in this case the record reflects that a consensus to approve the PMA was reached, an appropriate resolution

[6] During the key period of the Carestream review, the CDRH SOP on resolving scientific disagreements was entitled *Standard Operating Procedure (SOP) for Resolution of Internal Differences of Opinion in Regulatory Decision-Making* (Oct. 30, 2009).

of a scientific disagreement does not require consensus. It requires that all viewpoints be heard and that the decision-maker reaches a reasonable conclusion in light of all viewpoints and the scientific evidence before the Agency.

In this case, the FDA review of the PMA file showed that the reviewers' concerns were given a lengthy, thorough, and fair hearing and that reliance on FDA mammography experts to help resolve the scientific disagreement was appropriate. The PMA file amply records the nature of the scientific disagreements and their resolution. In addition, the record reflects that the Lead Reviewer, who had originally recommended against approval, ultimately changed his mind and agreed with the decision to approve the PMA based on the clinical and statistical conclusions of the experts in these areas, as reflected in meeting minutes and his signed approval recommendation in the administrative record. The documents in the PMA file indicate that he accepted this resolution, and he chose not to take advantage of the procedures in place at the time to initiate a formal appeal of this or any intermediate decision. Even if he had been dissatisfied with the decision, however, the PMA record provides more than enough evidence to support a decision by CDRH to approve the Carestream PMA. As noted above, appropriate resolution of scientific disagreements does not require consensus. It requires that all viewpoints are given reasonable consideration and that the ultimate decision is based on adequate scientific evidence consistent with the appropriate regulatory standard.

2. Allegations of procedural violations

The original referral letter alleged three procedural violations in the review of the Carestream device:

(i) It was a violation of "FDA regulations governing the proper approval process" for the Deputy Director of the OIVD to seek expert consults on a review issue, and for those experts to be managers from another division outside ODE who had not been device reviewers;

(ii) The Deputy Director's June 18, 2010 request that Carestream submit images from six patients who did not have cancer to address the microcalcification issue violated FDA regulations by "circumventing the April Not Approvable letter in the absence of any appeal or other legitimate reason"; and

(iii) The Deputy Director failed to memorialize his actions described in (2) by placing documentation in the administrative file, in violation 21 CFR § 10.70.

With respect to the first allegation, the 2012 FDA report found that there are no regulations or any other legal requirements prohibiting or restricting the use of agency experts from either outside the review team or who had not been medical device reviewers. The report also found that the use of agency mammography experts (of whom there were none on the review team) to help resolve internal disagreements about a mammography device was consistent with sound review practice and with FDA's statutory responsibility.

With respect to the second allegation, the 2012 report found that there are no laws, regulations, or other rules that preclude FDA from revisiting or altering a request in a Not Approvable letter. In addition, the report found that the PMA record showed that the Deputy Director's request followed a sequence of communications with the company and inside FDA seeking additional images from Carestream to resolve the disagreement regarding subjective preference data relating to microcalcifications.

With respect to the third allegation, the 2012 report found that the PMA did not contain a formal document entitled "minutes" of the June 18, 2010, call, but did contain an email from the Deputy Director to the review team and one of the mammography experts informing them of the call and detailing the images requested from Carestream. The report observed that while FDA's regulations are not specific about which communications should be memorialized, the OIG report recommended that a PMA file include "the contents and dates of any phone call or other meetings between FDA reviewers and the company." The 2012 FDA report concluded that "the documentation in the file of this telephone call, although not ideal, provided substantial compliance with 21 CFR § 10.70, and did not violate or appear to violate any law, regulation, or rule."

The May 31, 2012, referral letter did not allege any other potential violations of laws or regulations governing the review of the Carestream PMA.

III. New questions

OSC's March 14, 2014, email sets out a number of new questions concerning the procedural history of the original Carestream PMA review. It does not allege any new violations of applicable laws or rules or raise any new scientific issues. Most of the questions in the March 14, 2012 email appear to be directed at FDA. Questions 8 and 13 seek additional information about FDA's findings on the original allegations. Questions 4-7, 10, 12, 14, and 15 seek copies of documents in the Carestream PMA file or ask for detailed explanations of the actions and beliefs of reviewers and supervisors at various points during the Carestream PMA review.

Question 2 seeks information about the decision to transfer responsibility for assessing the scientific and technical aspects of this matter from OIG to FDA. The decision was made by the Secretary, after receiving 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 has informed FDA that her decision was based on two factors. First, due to the complexity of both the scientific and regulatory issues raised by the allegations, and the need to evaluate (under 5 U.S.C. § 1213(d)(4)) whether there was any "violation or apparent violation of any law, rule, or regulation," the Secretary determined that FDA was the only HHS component that had the necessary combination and scientific and regulatory expertise. Second, the Secretary recognized that the review of the scientific and regulatory issues must be objective and independent of FDA officials who had been involved in the prior reviews. Therefore, the Secretary asked the Commissioner to address, in detail, the issues that were not covered by OIG, and to ensure that the review was conducted exclusively by scientific and regulatory staff in the Office of the Commissioner, not by any staff who were involved in prior FDA decisions on the devices in question or staff from CDRH.

OIG has written a separate supplemental report in answer to questions 1, 3, 11, and 15, which pertain to its original investigation and report. The OIG report is included as Attachment B.

In the following sections, FDA offers answers to the questions directed at FDA, organized into the following two categories: (1) questions related to specific findings in the 2012 report; and (2) questions requesting documents or explanations of the actions and beliefs of participants in the Carestream decision.

A. Questions related to specific findings in the 2012 FDA report

Q8: *Provide an explanation as to the basis for the determination that the submission and review of six breast images, none of which contained malignancies, could satisfy the deficiencies set forth in the Not Approvable Letter. Who participated in this decision? Was the decision documented in the administrative file? If so, please provide a copy of the documentation memorializing the decision.*

A: This question appears largely to restate the second procedural allegation in the 2012 referral letter. As described in the 2012 FDA report, an FDA mammography expert, brought in to resolve continuing questions about safety and effectiveness of the Carestream device and the relevance of the preference analysis, considered this issue and determined that as long as microcalcifications were present and these could be adequately visualized with the images produced by the Carestream device, it was not relevant if the microcalcifications were present in malignant or benign cases. The preference analysis addressed whether reviewers preferred digital images or plain film to view microcalcifications (and other features), irrespective of whether those features resided in mammograms of breasts determined to have or not have cancer. After reviewing the Carestream images of microcalcifications, the mammography expert concluded that the visualizations of microcalcifications were of high enough quality to detect microcalcifications and to use them in a final mammography report, and she recommended approval of the device. According to the minutes of the July 23, 2010 meeting, the mammography expert and the statistician explained their conclusions that the device was safe and effective, after which the Lead Reviewer concluded that the issues surrounding the subjective preference data had been adequately addressed and recommended approval of the application. Accordingly, FDA approved the application. (Attachment C.)

As explained in the 2012 report, FDA has discretion to revisit or revise the deficiencies or requests in a Not Approvable letter. There is no law or regulation that prohibits the agency from reconsidering aspects of a Not Approvable letter. There was ample evidence in the PMA that the scientific issues raised in the Not Approvable letter were thoroughly considered and resolved before the approval. CDRH was therefore not required to "satisfy the deficiencies set forth in the Not Approvable Letter" before approving the Carestream PMA. FDA's rules also do not specify a particular procedure for modifying the information needed following a Not Approvable letter. Therefore, no specific determination of the kind sought in the question was required, and no rules were violated by the process that was followed. The July 23 meeting minutes document agreement within the review team that the information submitted on the issue of

microcalcifications was sufficient to address the concerns that had been raised in the Not Approvable letter.

> Q13: *Page 30 of the FDA report contains a reference to section 10.70 of title 21 of the Code of Federal Regulations which mandates that FDA administrative files should include minutes of meetings pertinent to significant agency decisions. The OIG report found that FDA did not document minutes from nine meetings with Carestream and four consultations with FDA staff. Rather than accurately restating this finding, the FDA report stated that the administrative file did not contain minutes from "several" meetings. The report concluded that the documentation in the file, "although not ideal, provided substantial compliance with the regulation." Commissioner Margaret Hamburg's cover letter described the missing minutes as a "small number of documentation errors." Please provide the rationale for the conclusion that, although the file did not include formal minutes from more than a dozen meetings (the content and outcome of which appears to have had a significant impact on the deliberative process and ultimate outcome of the approval of the Carestream device), the failure to include the minutes in the file did not violate a regulatory section specifically requiring inclusion of the minutes in the file.*

A: This question mischaracterizes both the 2012 FDA report and 21 CFR § 10.70. The quote from the report that certain documentation "although not ideal, provided substantial compliance with the regulation," was not about the Carestream PMA file as a whole. As described above in section I.b.ii., the quoted language was about whether an email describing a single phone call between FDA and the sponsor satisfied the requirements of 21 CFR § 10.70 relating to documentation of significant agency decisions.[7]

The question also inaccurately states that § 10.70 specifically required inclusion of the missing minutes in the file. As described in the 2012 reports from FDA and OIG, 21 CFR § 10.70 does not by its terms require minutes of any specific types of PMA-related meetings. The regulation also does not specify any consequence for failure to follow its requirements. 21 CFR § 10.70 requires that FDA employees responsible for handling a matter are responsible for the completeness of the administrative file on each "significant FDA decision." The file must contain "appropriate documentation of the basis for the decision," including "relevant evaluations, reviews, memoranda, letters, opinions of consultants, minutes of meetings, and other pertinent written documents." This is a general regulation applicable to all of FDA's myriad regulatory decisions, and does not purport to define which meetings that occur in the course of a single type of medical product review are relevant or require meeting minutes.

As OIG pointed out in its report, at the time of the Carestream review, FDA had not itself defined: (1) what constituted a "significant FDA decision as it relates to the device approval or clearance process"; or (2) the specific documents that should be in the PMA file.[8] The OIG

[7] The question also implies that the term "several" was somehow inaccurate. "Several" is an indefinite term, generally defined as "more than two and less than many." See http://www.merriam-webster.com/dictionary/several; http://www.oxforddictionaries.com/us/definition/american_english/several.

[8] Subsequent to the approval of the Carestream PMA, FDA issued an internal SOP and created a training module on appropriate documentation in the administrative file. CDRH SOP: *Compiling the Administrative File for Premarket*

stated that "for purposes of its review" it considered the decision to approve a device "significant" and its view that a PMA file should "reasonably include" "the contents and dates of any phone calls or other meetings between FDA reviewers and the sponsor" and the "the contents and dates of any internal FDA discussions or consultations, or emails concerning device clearance." The current view of OIG on this issue, while helpful on the issue of good administrative practice, does not constitute a statutory or regulatory requirement and therefore could not have been violated during the period in question.[9]

In fact, the OIG emphasized that it "found that most of the documents [the OIG] determined should reasonably be included in the administrative files for the referenced devices in the complainant's allegations were present," and that any "missing documents do not necessarily indicate that FDA's decisions to approve or clear the devices were not supported by other documentation in the file." As a result, the failure to include certain documents entitled "minutes of meetings" documenting the meetings with the sponsors and the internal discussions, while perhaps not optimal administrative practice, cannot be said to have violated any existing law, regulation, or even standard operating practices (SOPs). In addition, the alleged lack of documentation provides no legal basis for invalidating the Agency's approval, which was based on objective, scientific evidence.

In the context of a PMA, the Lead Reviewer is responsible for establishing a complete administrative file in accordance with § 10.70. In this case, a document in the PMA file shows that the Acting Division Director was concerned that the Lead Reviewer had not compiled a complete administrative file. For example, the Acting Director found that the file included clinical reviews from Dr. Smith, the original medical reviewer, but not the clinical reviews from the senior mammographer.

B. Requests for documents and/or explanations of the actions and beliefs of participants

Some of the remaining questions ask FDA to produce documents from the PMA file, which contains confidential commercial information and trade secrets. FDA has produced any existing responsive documents in the PMA file that are not prohibited by law from release. Some of the questions seek, in addition to or in the alternative to documents in the PMA, descriptions and explanations of events and motivations that are not clearly documented in the PMA file.

In conducting the initial review of the OSC referral letter, FDA considered whether interviewing participants in the PMA review would produce information relevant to responding to the allegations within the scope of 5 U.S.C. § 1213(c). At that time, FDA concluded that none of the scientific or procedural allegations raised any issues that could be resolved by the testimony of

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Submission Decisions, Version 1.0, (effective September 20, 2012), as referenced in DHHS, OIG, *FDA's Clearance of Medical Devices through the 510(k) Process*, September 2013, OEI-04-10-00480.

[9] We note further that § 10.70 vests substantial discretion in the agency to determine which decisions are sufficiently "significant" to require documentation; what documentation is "appropriate"; and the "completeness" of the administrative file. *See Auer v. Robbins*, 519 U.S. 452, 461 (1997) (agency interpretation of its own regulations is entitled to controlling weight unless plainly erroneous).

the participants. Whether there was an adequate scientific basis to find the Carestream device safe and effective could be fully evaluated within the four corners of the PMA file, since all the data on which FDA relied was in the file and the reviewers had amply documented their views and concerns about the data in the file. Similarly, whether the three procedural allegations described in section I.b.i., above, gave rise to violations of applicable laws or other rules did not require testimony. Those issues could be resolved solely by reference to the evidence in the file and the laws and rules under which FDA operates. FDA therefore concluded that it was unnecessary to go beyond the information in the PMA file.[10] Indeed, the questions concerning descriptions of events and motivations of participants that cannot be answered by examining the PMA file fail to assert a connection between the information sought and the violations alleged under 5 U.S.C. § 1213(c) in the May 31, 2012, letter.[11] In addition, even if there were some marginal benefit to seeking such testimony, FDA is constrained from doing so in view of the related pending litigation and other parallel proceedings.

1. Q4: *Provide specifics regarding the nine meetings and four consultations referenced but not formally documented in the administrative file for the Carestream Mammography device, including dates, locations, participants, content, conclusions/findings, and actions taken as a result of these meetings.*

A: Information about these meetings and consultations is found in Attachment D.

2. *Q5: Provide specific information regarding the August 25, 2009, meeting described as an "informal Request for Reconsideration." Where was this meeting held and who was present? Please provide a summary of the subject matter and outcome of the meeting. Please provide us with a copy of the minutes, if any, of the meeting. If minutes for the meeting do not exist, please provide the documentation contained in the file that references the August 25, 2009, meeting.*

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[10] It is worth noting that a court would review a challenge to an FDA decision to approve a device PMA on the record under the deferential standard of the Administrative Procedure Act. Any challenge to an Agency decision is to be reviewed by the court based solely upon the administrative record before the Agency at the time the decision was rendered. No additional testimony is necessary. Moreover, under the APA deferential standard of review, the court reviewing the relevant administrative record is not empowered to substitute its judgment for that of the agency. *Citizens to Preserve Overton Park, Inc. v. Volpe*, 401 U.S. 402, 416 (1971) ("The court is not empowered to substitute its judgment for that of the agency" and may reverse only when "there has been a clear error of judgment"); *see also Serono Labs., Inc. v. Shalala*, 158 F.3d 1313, 1320 (D.C. Cir. 1998) (FDA's determination of a product's safety and effectiveness rests squarely on its "'evaluation of scientific data within its area of expertise'," and thus FDA is "entitled to a 'high level of deference' from this court") (citing *A.L. Pharma, Inc. v. Shalala*, 62 F.3d 1484, 1490 (D.C. Cir. 1995)). The relevant inquiry is not whether a reviewer would have made a different decision, but whether based on the administrative record at the time of the approval decision there was substantial evidence supporting the decision. In conducting its investigation, the OIG itself recognized this standard by emphasizing that, as an independent investigative agency, it "may not substitute its judgment and overrule discretionary decisions made by agency officials with responsibility for HHS programs." As discussed in the 2012 report and in this Supplemental Report, there was ample objective, scientific evidence in the administrative record to support the Agency's approval decision.

[11] Under 5 U.S.C. 1213(c), an agency head is not required to conduct an investigation or report on allegations that are not related to a "positive determination" by the Special Counsel.

A: The PMA file contains a document entitled Carestream Meeting Memo, describing a meeting between two representatives of Carestream and seven CDRH representatives, on August 25, 2009. (See Attachment E.) The CDRH representatives were Janine Morris, Toby Lowe, Michael O'Hara, Robert Smith, Paul Hardy, Tom Gwise, and Jeff Shuren. The meeting concerned the sponsor's request for reconsideration of the April 9, 2009 Not Approvable decision on their PMA. According to the minutes, the outcome of the meeting was that the Agency agreed to consider the request and respond within two weeks. Possible outcomes discussed at the meeting included maintaining the Not Approvable decision or reconsideration, resulting in an Approvable letter, a Major Deficiency letter, or an Approval order.

3. Q6: *On page 8 of the OIG report, there is a reference to a meeting between FDA and Carestream, after which a member of the review team emailed the review team supervisor to request the meeting minutes. This email, according to the report, was included in the administrative file but neither the minutes from the actual meeting nor a response to the review team member's email request was found. Please provide details as to when this meeting occurred and who was in attendance. Please describe the conclusions/findings, and actions taken as a result of this meeting.*

A: This was a phone call on June 18, 2010 between the Acting Division Director, the Lead Reviewer, and the sponsor. According to the email and the Lead Reviewer's August 16, 2010 memorandum recommending approval of the PMA, which describes this meeting in some detail, FDA requested that the sponsor submit four images each from six patients, some of which should include microcalcifications, and which the senior mammography expert said would be sufficient. The sponsors did so. These images were reviewed by the senior mammography expert, who concluded that they were of adequate quality to make diagnoses.

4. Q7: *In an April 7, 2010, memo, Mr. St. Pierre set forth his determination that he was "not comfortable" with the Lead Reviewer's approach regarding the Carestream devices' capability in detecting and defining microcalcifications. Please provide a copy of this email and an explanation as to the basis for Mr. St. Pierre's determination.*

A: A copy of this document is attached as Attachment F. Further information about the basis for Mr. St. Pierre's statement is not in the PMA file.

5. Q9: *There seems to be conflicting information regarding the June 18, 2010, meeting between Carestream and FDA. Provide details regarding the meeting, including identifying the participants, whether the meeting was conducted by telephone or in person, and the content and outcome of the meeting. Were minutes of the meeting created and placed in the administrative file? If so, please provide a copy of the minutes. If not, please provide the documentation in the file that references the June 18, 2010, meeting.*

A: This is the same meeting described in Q6 in #3 above for which there were no meeting minutes, but which is described in the Acting Director's email and on page 14 of the Lead Reviewer's memo of August 16, 2010. (A copy of the latter is attached as Attachment G.)

6. Q10: *Describe in detail any and all communications Mr. St. Pierre or any FDA official who was not a member of the Carestream Review Team had with Carestream officials regarding this PMA application.*

A: The only example of such a communication that we encountered in the PMA file is the June 18, 2010 telephone call described in response to Q6 in #3 above.

7. Q12: *Provide testimony from members of the Review Team as to their version of the Carestream application review; specifically, determine whether the review team members felt coerced or otherwise pressured into approving Carestream's application.*

A: See discussion of issues surrounding the taking of interviews in section III. B, at page 14 of the Supplemental Report. There are additional reasons for not taking testimony on the issue of possible coercion. First, some of the reviewers have now filed a lawsuit against FDA that includes allegations of coercion related to the Carestream PMA review. The pending litigation's constraints with respect to the rights of individuals and governmental legal prerogatives preclude the Agency from seeking, in a separate proceeding, testimony related to matters involved in the litigation.

Second, there is no documentary evidence that the reviewers alleged coercion during the PMA review, despite many opportunities to do so. The PMA file shows that the reviewers repeatedly documented their scientific views and disagreements with supervisors and other reviewers, and yet did not document feeling coerced or otherwise pressured to approve the PMA. In addition, CDRH had in place at the time of the PMA review a clear policy on internal disagreements about scientific and regulatory issues.[12] The policy established a process for handling disagreements between reviewers and managers, and authorized appeals to higher levels of management if the reviewers were unsatisfied with the resolution of the disagreement. None of the reviewers of the Carestream PMA initiated the process for resolving disagreements provided for in the policy, nor did anyone initiate an appeal of the approval decision.

Third, the issue of the reviewers' feelings about the scientific disagreement was not raised in the May 31, 2012, referral letter and does not pertain to any specific allegations of a violation of law, rule, or regulation identified in the referral letter or in the March 14, 2014 questions.

8. Q14: *According to the whistleblower, Mr. St. Pierre sent an email to the Lead Reviewer and Statistician on the Carestream device review team on August 16, 2010, stating that, "no one is to contact the sponsor...." The whistleblower contends that the email was sent after the Lead Reviewer and Statistician expressed concern about the content of the proposed labeling on the Carestream device. Was such an email issued? If so, please provide a copy of this email, as well as an explanation as to Mr. St. Pierre's purpose and goal in issuing this directive.*

[12] CDRH, *Standard Operating Procedure (SOP) for Resolution of Internal Differences of Opinion in Regulatory Decision-Making*, October 30, 2009.

A: We have not found this email in the PMA file, or any other information related to such an email.

9. Q15: *According to the whistleblower, the Lead Reviewer felt "pressured and bullied" into recommending that the device be found safe and effective at a July 23rd meeting. Are minutes from this meeting contained in the administrative file? If so, please provide a copy of these minutes. Was the Lead Reviewer interviewed pursuant to either the OIG investigation or the FDA investigation? If not, why? If so, please provide a copy of his testimony regarding his version of the July 23rd meeting specifically and, generally, his opinion regarding the review and approval process for the Carestream device.*

A: The minutes of the July 23 meeting are contained in the file. (Attachment C.) The Lead Reviewer was not interviewed as part of the FDA investigation. As described above, FDA considered whether interviews of those involved in the PMA review would be relevant to answering the allegations in the referral letter, and concluded that none of the scientific or procedural allegations raised any issues that could be resolved by the testimony of the participants. (There were no allegations of coercion or bullying in the referral letter.)

Nevertheless, the PMA file contains the Lead Reviewer's comments on the draft minutes of the meeting, which are instructive on his contemporaneous view of the meeting. He revised the wording of some of the statements attributed to him, but his changes do not reflect any significant difference in the tone of the meeting or any statement that he did not agree with the ultimate resolution. His version includes the following description of own statements at the meeting: "Paul said that he thinks the issue in regards to the microcalcifications has been addressed by the consultants now on the file....Paul said he would recommend approvable based on the consultants' recommendations."[13] We are providing a copy of this document. (Attachment H.)

[13] In response to the Lead Reviewer's suggested revisions of the minutes, the Acting Director sent him an email stating that "I incorporated what I could from your edits, but a number of the edits you made appeared to rewrite what was actually said at the meeting. Since I was not able to incorporate all of your changes, I included your redlined version of the minutes in the administrative record."

Attachment A

THE SECRETARY OF HEALTH AND HUMAN SERVICES
WASHINGTON, D.C. 20201

October 1, 2012

Ms. Carolyn Lerner
Special Counsel
U.S. Office of Special Counsel
1730 M Street, N.W. Suite 300
Washington, D.C. 20036-4505

Dear Ms. Lerner:

This letter is in further response to your referral of May 31, 2012, (OSC referral DI-11-3325), requesting the Department of Health and Human Services' (HHS) review of whistleblower allegations under 5 U.S.C. § 1213, concerning the Food and Drug Administration's (FDA) review of certain applications for pre-market approval or clearance of certain medical devices.

Initially, I referred the matter to the HHS Office of Inspector General (OIG) to investigate all of the allegations contained in the May 31, 2012, referral. However, OIG declined to assess scientific and regulatory program issues that exceed OIG's scientific expertise and statutory authority. Therefore, I asked the Commissioner of Food and Drugs to investigate and report on the allegations, including a review of the OIG findings and the scientific and regulatory program issues not addressed by OIG. The review was conducted by scientific and regulatory staff in the Office of the Commissioner who were not involved in prior FDA decisions on the devices in question. Enclosed are the OIG report, the FDA report, and a transmittal letter from the Commissioner of Food and Drugs, which I have reviewed and am transmitting, pursuant to 5 U.S.C. § 1213(d).

Sincerely,

Kathleen Sebelius

Kathleen Sebelius

Enclosures

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

TO: Kathleen Sebelius
Secretary

FROM: Margaret A. Hamburg, M.D.
Commissioner of Food and Drugs

SUBJECT: Commissioner of Food and Drugs' Response to the U.S. Office of Special Counsel Referral (OSC File No. DI-11-3325)

The attached report responds to your request for a review of certain whistleblower allegations described in a letter from the Office of Special Counsel dated May 31, 2012. The whistleblower makes the following allegations:

1) FDA reviewers used the agency's 510(k) review process to assess colonography software devices that required a more stringent level of review prior to clearance;

2) The improper clearance of the devices led to their use on asymptomatic patients, potentially exposing millions of otherwise healthy people to unnecessary radiation and creating a significant increased cancer risk; and

3) FDA reviewers approved a specific digital mammography system for use despite the fact that the manufacturer failed to provide adequate clinical data to support the safety and effectiveness of the system after its original application was found deficient.

You asked that we review certain aspects of the first allegation, and the second and third allegation. The Office of the Inspector General (OIG) also investigated aspects of the first allegation. We have reviewed the findings of the OIG as part of this review.

In evaluating the allegations, we have reviewed the available information on each of the decisions and actions that form the basis of the allegations.[1] We considered, pursuant to the standard in 5 U.S.C. § 1213(d), whether these decisions or actions violate or appear to violate any law, regulation, or rule administered by the Food and Drug Administration (FDA).

Summary of the Review

1. In response to the first allegation, the review concluded that FDA reviewers properly used the 510(k) process to assess CT colonography devices for asymptomatic screening. The review found that CDRH's decisions related to the intended use of these devices were consistent with the statute and regulations. The review also found that there were minor documentation errors, but these did not call into question the legal or scientific basis of the 510(k) in question.

[1] The review was conducted by scientific and regulatory staff in the Office of the Commissioner (OC) who were not involved in prior FDA decisions on the devices in question.

2. In response to the second allegation, we found that the Center for Devices and Radiological Health (CDRH)'s conclusion that the benefits of CT colonography for asymptomatic screening outweigh its risks was based on a thorough and appropriate evaluation of the risks. Their assessment included a comparison of the advantages and disadvantages of both CT colonography and colonoscopy, including the risks associated with each method, the number of cancers that could be prevented with universal screening, the currently low rates of screening with colonoscopy, and the likelihood that having CT colonography available as an option will increase the number of Americans who undergo screening. CDRH's conclusion that the benefits of the device outweigh the small radiation risk is supported by a growing number of medical societies and insurers. Some other groups have concluded to the contrary, but most of these conclusions are several years old, and the data supporting CT colonography for screening has increased in that period.

The review also found no significant basis for the whistleblower's allegation that the use of CT colonography for asymptomatic screening is likely to result in an increase of 7,000 cases of colon cancer per year. The whistleblower did not provide the assumptions or scientific information supporting this claim. It is unlikely, however, that the whistleblower's estimate takes into account the number of colon cancers that would be prevented by the early detection of pre-cancerous polyps through CT colonography, or other factors associated with an adequate risk-benefit analysis. A recent, well-designed risk-benefit analysis directly compared the risks of radiation-induced cancers against the benefits of preventing cancers using CT colonography, and found that CT colonography would prevent 24-35 times as many cancers as it could induce. To FDA's knowledge, none of the outside scientists or groups who have studied or reviewed CT colonography, including those who have expressed concern about the radiation risk, have suggested that the technology would result in a net increase in the number of colon (or other) cancers.

3. In response to the third allegation, which focused on a specific digital mammography device, the review concluded that the device was appropriately found to be safe and effective on the basis of valid scientific evidence. The specific study result about which the whistleblower had concerns did not undermine the overall finding of safety and effectiveness. The review also found that procedures followed in the review of the device did not violate or appear to violate any laws, regulations, or rules, and that the small number of documentation errors did not call into question the legal or scientific basis of the PMA approval.

Advisory Committee Meeting on CT Colonography

Colorectal cancer is the second leading cause of cancer deaths in the U.S. and colorectal screening of all adults over 50 years old could cut the number of colorectal cancer deaths in the US by more than half. Yet screening rates remain relatively low, in part because many patients are reluctant to undergo colonoscopy. Having available other safe and effective screening options is therefore an important public health goal.

As described above, CDRH concluded in 2009 that the benefits of CT colonography as an option for screening outweighed its risks, and the report finds that they reached this conclusion on the basis of an appropriate and well-supported evaluation. Scientific research on the risks and benefits of CT colonography has steadily increased since the first CT colonography software was cleared for asymptomatic screening and has strengthened support for the conclusion that CT colonography is an effective screening method and that its benefits outweigh its risks. FDA,

manufacturers, and researchers have also taken steps to lower the radiation dose needed for effective screening. I am therefore confident that CDRH's conclusion remains sound.

Several comprehensive reviews of the risks and benefits of the technology were conducted by outside groups in 2008-2009, with differing results. New research continues to confirm the effectiveness of CT colonography for screening, and indicates that the availability of CT colonography increases the total number of individuals who will get screened. In addition, radiation doses have come down since the technology was introduced, and recent research indicates that radiation doses can be reduced even further. Despite the accumulating evidence and increasing acceptance of CT colonography for screening in the healthcare community, few comprehensive reviews of both risks and benefits have been conducted since 2008-2009.

To facilitate the agency's consideration of the evolving research on performance characteristics, usefulness in specific populations, and data on the lowest effective radiation dose, I intend to exercise my discretion, under 21 CFR § 14.1(a)(1), to hold an advisory committee meeting to obtain expert review of current data on the risks and benefits of these devices for screening. The meeting would inform FDA's continuing regulation of these devices. The panel meeting would also provide an opportunity for a public discussion of these issues, and would allow interested parties to provide their views.

The whistleblower allegations surrounding a specific manufacturer's digital mammography device questioned whether the manufacturer provided sufficient clinical data to establish the safety and efficacy of that particular device. We have completed our review and have not identified issues related to digital mammography that would benefit from further study by an advisory committee.

If you have any questions about this report, please contact me, or your staff may contact Peter Lurie, M.D., M.P.H., Acting Associate Commissioner for Policy and Planning, at (301) 796-7527, or by email at Peter.Lurie@fda.hhs.gov.

Margaret A. Hamburg

Margaret A. Hamburg, M.D.
Commissioner of Food and Drugs

Attachment: Review of Whistleblower Allegations

Review of Whistleblower Allegations

Office of the Commissioner

U.S. Department of Health and Human Services

U.S. Food and Drug Administration

October 1, 2012

Review of Whistleblower Allegations

This review by the Office of the Commissioner, FDA, responds to a request from the Secretary to review certain whistleblower allegations described in a letter from the Office of Special Counsel dated May 31, 2012 (OSC File No. DI-11-3325). The allegations relate to the clearance of CT colonography devices for screening of asymptomatic patients and to the approval of a digital mammography device.

The whistleblower makes the following allegations:

1) FDA reviewers used the agency's 510(k) review process to assess colonography devices that required a more stringent level of review prior to clearance;

2) The improper clearance of the devices led to their use on asymptomatic patients, potentially exposing millions of otherwise healthy people to unnecessary radiation and creating a significant increased cancer risk; and

3) FDA reviewers approved a specific digital mammography system for use despite the fact that the manufacturer failed to provide adequate clinical data to support the safety and effectiveness of the system after its original application was found deficient.

We were asked to review aspects of the first allegation, as well as the second and third allegation. Upon the request of the Secretary, the Office of the Inspector General (OIG) also investigated aspects of the first allegation. We have reviewed the findings of the OIG as part of our review.

In evaluating the allegations, we reviewed available data and information on these clearances and approvals as well as published literature and information on CT colonography for screening. We have also considered, pursuant to the standard in 5 U.S.C. § 1213(d), whether the actions that form the basis of the allegations violate or appear to violate any law, regulation, or rule administered by the Food and Drug Administration (FDA).

Summary of Findings

1. In response to the first allegation, we concluded that FDA reviewers properly used the 510(k) process to assess CT colonography devices for asymptomatic screening. We found that CDRH's decisions related to the intended use of these devices were consistent with the statute and regulations. We also found, on the basis of the OIG review, a small number of documentation errors, but these did not call into question the legal or scientific basis of the 510(k) in question.

2. In response to the second allegation, we found that the Center for Devices and Radiological Health (CDRH)'s conclusion that the benefits of CT colonography outweigh its risks was based

on a thorough and appropriate evaluation of the risks and benefits of CT colonography for screening of asymptomatic patients. An appropriate benefit-risk assessment is complex and requires an assessment of comparable alternatives and unmet medical needs as well the specific risks and benefits of the device standing alone. Here, colorectal cancer is the second leading cause of cancer deaths in the U.S. and colorectal screening of all adults over 50 years old could cut the number of colorectal cancer deaths in the U.S. by more than half. Yet screening rates remain relatively low, in part because many patients are reluctant to undergo colonoscopy. Having available other safe and effective screening options is therefore an important public health goal. To carry out its evaluation, CDRH appropriately reviewed the advantages and disadvantages of both CT colonography and colonoscopy, including the risks associated with each method, the number of cancers that could be prevented with universal screening, the currently low rates of screening with colonoscopy, and the likelihood that having CT colonography available as an option will increase the number of Americans who undergo screening.

FDA's conclusion that the benefits of the device outweigh the small radiation risk is supported by a growing number of medical societies and insurers, although some other groups have concluded that there was insufficient information to conclude that the benefits outweigh the risks. Since the majority of those reviews were conducted in 2008-2009, scientific research confirming the effectiveness of CT colonography for screening has steadily increased, as has research indicating that the availability of CT colonography increases the total number of individuals who will get screened. FDA, manufacturers, and researchers have also taken steps to lower the radiation dose needed for effective in CT colonography.

We also found no significant basis for the whistleblower's allegation that the use of CT colonography for asymptomatic screening is likely to result in an increase of 7,000 cases of colon cancer per year, or that the risk of CT colonography outweigh the benefits. The whistleblower did not state his or her assumptions or provide scientific evidence to support this assertion. It is unlikely that the estimate takes into account the number of colon cancers that would be prevented by the early detection of pre-cancerous polyps through CT colonography, or other factors associated with an adequate risk-benefit analysis. A recent, well-designed risk-benefit analysis directly compared the risks of radiation-induced cancers against the benefits of preventing cancers using CT colonography, and found that CT colonography would prevent 24-35 times as many cancers as it could induce. To FDA's knowledge, none of the outside scientists or groups who have studied or reviewed CT colonography, including those who have expressed concern about the radiation risk, have suggested that the technology would result in a net increase in the number of colon (or other) cancers.

3. In response to the third allegation, which focused on a specific digital mammography device, we concluded that the device was appropriately found to be safe and effective on the basis of

valid scientific evidence. The specific study result about which the whistleblower had concerns did not undermine the overall finding of safety and effectiveness. We also found that procedures followed in the review of the device did not violate or appear to violate any laws, regulations, or rules, and that the small number of documentation errors did not call into question the legal or scientific basis of the PMA approval.

4. We describe recent actions of the Center for Devices and Radiological Health (CDRH) designed to clarify and strengthen procedures related to the review of medical devices.

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Glossary of acronyms used in the report

CDRH: Center for Devices and Radiological Health, FDA
CFA: Comparative Feature Analysis
CT: Computed tomography
ERS: Enriched Reader Study
FDA: Food and Drug Administration
OC: Office of the Commissioner, FDA
ODE: Office of Device Evaluation, CDRH, FDA
OIG: Office of Inspector General, DHHS
OSB: Office of Surveillance and Biometrics, CDRH, FDA
PMA: Premarket Approval

I. Regulatory Framework for Approval and Clearance of Medical Devices

FDA has two principal premarket review processes for medical devices: the premarket approval (PMA) process and the 510(k) clearance process. Which process is used depends on the device's classification and similarity to already marketed devices. PMA review, which is the most stringent form of premarket review, is reserved by statute for devices classified in Class III, the classification for high-risk devices, and for devices that are not "substantially equivalent" to devices already on the market. To obtain PMA approval, a device manufacturer must submit evidence providing reasonable assurance that the device is safe and effective for its intended use. 21 U.S.C. § 360e.

The 510(k) process is a less-stringent form of premarket review. By statute, devices are eligible for 510(k) clearance if they are: (1) in Class I or Class II, the classifications for lower-risk devices, and in some cases Class III devices; and (2) showed to be "substantially equivalent to an already marketed ("predicate") device. 21 U.S.C. § 360c(f). A device may be found to be "substantially equivalent" to a predicate device if it has the same "intended use" and technological characteristics as the predicate device. FDA may also determine that the device is substantially equivalent to a predicate device if both devices have the same intended use but different technological characteristics and the manufacturer submits information showing that that the new device is at least as safe and effective as the legally marketed device. In either case, the manufacturer must show that the new device does not raise different questions of safety and effectiveness. 21 U.S.C. § 360c(i). If the device is found not substantially equivalent to the

predicate, it must go through the PMA process or a "de novo" review, which is also more stringent than the 510(k) process, in order to be marketed.

The authority to approve a PMA and clear a 510(k) rests with officials in CDRH. These officials review the scientific evidence submitted by the manufacturer and determine whether the new device meets the legal requirements for approval or clearance.

II. Allegations Related to CT Colonography

A. Regulatory History

In 2002, CDRH cleared a 510(k) for the Viatronix 3D Colon, a CT colonography software device. The device's Indication for Use statement stated that the device was "for the purpose of patient screening for detection of colon cancers, polyps, masses, and other lesions." Shortly after K020658 was cleared, CDRH wrote a letter to Viatronix and other companies with similar claims, stating that the phrase "patient screening" was ambiguous. Because it could be read to mean "population screening," for which CDRH believed K020658 was not cleared, on May 15, 2002, CDRH asked the sponsor of K020658 to remove "patient screening" from the indication statement for its software device. Viatronix and the other companies did so, and substituted the phrase "screening a colon."

In late 2003, Viatronix submitted a large, government-sponsored, multi-center clinical study to CDRH to support the use of the device for screening of asymptomatic patients. The well-designed study found that CT colonography using the Viatronix device compared favorably with optical colonoscopy for screening asymptomatic patients. The sensitivity (rate of false negatives) of CT colonography was slightly better than colonoscopy and the specificity (rate of false positives) was slightly less but adequate. In 2004, CDRH cleared a 510(k) allowing Viatronix to include the phrase "patient screening" in its indication statement, having found that the study demonstrated the safety and effectiveness of the device for screening of asymptomatic patients.

CCI [redacted] Two medical reviewers argued that the change from diagnostic to asymptomatic screening created a new intended use, contending that the Viatronix device was never cleared to screen asymptomatic patients. These two reviewers also raised concerns about the risks to patients from CT scans used for asymptomatic screening, and argued that the risk of radiation exposure from repeated CT colonography outweighed its benefits. Other reviewers involved with the review argued that the benefits outweighed the risks.

CDRH reviewed the question of whether the change from diagnosis to asymptomatic screening created a new intended use and whether the 2004 Viatronix 510(k) should be rescinded. CDRH concluded at that time that the Viatronix 510(k) remained an appropriate predicate for asymptomatic screening, and declined to pursue rescission.

CDRH also conducted an evaluation of the risks and benefits of CT colonography devices in response to the concerns raised by two reviewers. The evaluation included scientific reviews of the clinical study that supported clearance of the Viatronix device (showing that the device compared favorably with colonoscopy in screening asymptomatic patients) as well as evaluations of the available evidence on the radiation risks associated with CT colonography.

CDRH's Office of Surveillance and Biometrics (OSB), which is separate from the part of CDRH that reviewed the 510(k)s in question, issued a report evaluating the available evidence on both the safety and the effectiveness of CT colonography. Their report included (1) a comprehensive review of all published clinical data on the effectiveness of the CT colonography compared to colonoscopy for screening; (2) an assessment of the radiation risk associated with CT colonography; and (3) a comparative assessment of the risks of perforation in colonoscopy and CT colonography, and the incidence of hemorrhage and infectious disease transmission with colonoscopy. OSB found that the effectiveness of CT colonography was roughly comparable to that of colonoscopy and that the radiation risk was small, but not zero. It was the unanimous view of the OSB review team that the benefits of CT colonography for screening were significant and that the radiation risk was justified. OSB observed that the radiation dose from CT colonography could be further reduced through measures such as optimization of the scan parameters and recommended that CDRH pursue reduction measures.

In 2010, CDRH also launched its "Initiative to Reduce Unnecessary Radiation Exposure from Medical Imaging," including CT scans.[1] The initiative recognizes that medical imaging has both led to improvements in diagnosis of numerous medical conditions, and, at the same time, exposes patients to ionizing radiation, which can increase the lifetime risk of developing cancer. The purpose of the initiative is to ensure that each patient receives only those imaging exams that are medically necessary, and that they receive the lowest possible radiation dose. CDRH is working with manufacturers to develop CT scanners and software that provide smaller doses of radiation and some of these are already on the market. CDRH is also developing dose reference standards for the minimum radiation dose necessary to generate images of sufficient quality for accurate diagnosis or screening. Working with other organizations, CDRH is also working on measures to better inform healthcare providers about radiation risks and how to reduce them, and to improve communication between healthcare providers and patients concerning the risks of radiation exposure.

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[1]FDA, Initiative to Reduce Unnecessary Radiation Exposure from Medical Imaging, available on line at http://www.fda.gov/Radiation-EmittingProducts/RadiationSafety/RadiationDoseReduction/default.htm.

B. Specific Whistleblower Allegations

Section II of the letter from the Special Counsel sets forth the whistleblower's allegations related to the clearance of CT colonography software devices for screening asymptomatic patients. Subsections II.A and B relate to the propriety of FDA's clearance of certain 510(k)s for CT colonography software under FDA's governing statute and regulations. Subsection II.C relates to whether the benefits of CT colonography outweigh its risks.

Section II.A ("Improper Clearance of Viatronix CT Colonography Devices for Population Screening") states that the whistleblower alleges that certain CT colonography software devices that were cleared under 510(k)s should instead have been approved under PMAs. The devices whose clearances the whistleblower questions are those whose 510(k)s cited the Viatronix V3D Colon software device as a predicate device for use in screening the colons of asymptomatic patients. The whistleblower alleges that the 510(k) for the Viatronix V3D Colon software device (K040126) could not serve as a predicate device for asymptomatic screening on four grounds:

1) The indication for use of the Viatronix CT colonography software was for "patient screening for detection of colon cancers, polyps, masses, and other lesions." The whistleblower alleges that FDA has never cleared or approved a CT scanner for use in screening of asymptomatic patients, so the phrase "patient screening" in Viatronix's indication for use could not have referred to screening of asymptomatic patients;

2) The whistleblower alleges that FDA's original interpretation of the phrase "patient screening" was that it did not refer to screening of asymptomatic patients. Instead, the whistleblower alleges that FDA interpreted "patient screening" to refer to screening of symptomatic patients;

3) The whistleblower alleges that the manufacturer of the Viatronix device failed to submit a 510(k) or receive clearance for the change in indication statement from "screening a colon" to "patient screening"; and

4) The whistleblower alleges that a change from a diagnostic indication ("screening a colon") to a screening indication was a new intended use that should have required the manufacturer of Viatronix CT colonography device to obtain a PMA approval rather than a 510(k) clearance.

We were asked to review the first and fourth of these specific allegations. The OIG reviewed the second and third allegation in section II.A of the referral letter.

Section II.B of the letter ("Failure to Properly Document Device Clearance Decisions Pursuant to 21 CFR § 10.70) states that whistleblower alleges that the clearance of K040126 was in error because the documentation in the administrative file was inadequate and violated 21 CFR § 10.70, FDA's regulation concerning documentation of agency decisions. In particular, the whistleblower alleges that there is no signed review memorandum in the administrative file or similar documentation showing an analysis of the predicate device.

Subsection II.C of the letter ("CT Colonography Scanning in Asymptomatic Patients Increases Cancer Risk") states that the whistleblower alleges that CT screening exposes a patient to x-ray radiation 800 times that of a chest x-ray, which presents an increased risk of cancer to the patient. The whistleblower alleges that the risk of cancer from CT colonography screening exceed its benefits for asymptomatic patients for whom the screening is unlikely to identify a serious disease.

C. Findings on the Allegations in Section II.A of the Referral Letter

1. Allegation Concerning the Cleared Indications for CT Scanners

Allegation: The Viatronix device could not serve as a predicate for asymptomatic screening because its cleared indication for use was for "patient screening for detection of colon cancers, polyps, masses, and other lesions." According to the whistleblower, FDA has never cleared or approved a CT scanner for use in screening of asymptomatic patients, so the phrase "patient screening" in Viatronix's indication for use could not have referred to screening of asymptomatic patients.

The OIG investigated this allegation and found that CT scanners are not listed as a predicate device in either the 2002 or 2004 Viatronix device 510(k) submissions.

We also reviewed the allegation to determine whether, as a regulatory matter, the fact that CT scanners themselves are not cleared for screening asymptomatic patients prevented FDA from clearing separate software devices for this indication.

a. Regulation of CT Scanners and CT Colonography Software Devices

Computed Tomography (CT) x-ray systems (CT scanners) are machines that use x-rays to show cross-sectional images or "slices" of areas of the body. CT scanners are classified in class II. *See* 21 CFR 892.1750 (device classification regulation). Manufacturers of CT scanners must comply both with the premarket clearance requirements and with performance standards for radiation-emitting products. CT scanners are generally cleared for very broad, non-disease specific indications for use, such as "for head and whole body X-ray Computed Tomography applications" or "to produce cross-sectional images of the body by computer reconstruction of x-

ray transmission data from either the same axial plane taken at different angles or spiral planes taken at different angles." The cross-sectional images produced by CT scanners are used for a variety of diagnostic and therapeutic purposes, although these purposes are not specifically listed in the device labeling.

A separate set of software devices may be used in conjunction with CT scanners to assist in the display and analysis of CT images, for specific diagnostic purposes. These software devices, known as picture archiving and communications systems, are separately classified in class II, and must comply with the premarket clearance requirements. *See* 21 CFR 892.2050 (device classification regulation). Software devices for use in displaying and analyzing CT images have been cleared under 510(k)s for a variety of indications related to the diagnosis of specific diseases and conditions.

Since the 1990s, software devices have been cleared for use in diagnostic evaluation of the colon with CT images. Traditionally, optical colonoscopy devices inserted into the colon have been used by physicians to diagnose and screen patients for diseases of the colon. Use of software devices to display CT images to evaluate the colon is a newer, non-invasive tool for diagnosing diseases of the colon and is referred to as CT colonography or virtual colonoscopy.

FDA has not cleared CT scanners or optical colonoscopes themselves for screening asymptomatic patients. FDA has, however, cleared software devices to be used with CT scanners and, separately, software to be used with colonoscopes, for screening both symptomatic and asymptomatic patients.

b. Legal Standard for Clearance of 510(k)s

A device may be lawfully cleared under a 510(k) if it is substantially equivalent to an appropriate predicate device. *See* 21 U.S.C. 360c(i)(1)(A). To determine whether the indications for CT scanners are relevant to the clearance of 510(k)s for CT colonography software devices, and to the Viatronix device in particular, we must determine whether CT scanners were the appropriate predicate devices for CT colonography software devices. The OIG determined that CT scanners were not listed as the predicate devices for either the 2002 or 2004 Viatronix device 510(k)s. The OC's review of these files confirms that both the manufacturer and CDRH regarded prior software devices rather than the scanners themselves as the appropriate predicate devices.

c. Conclusion

It is not relevant from a legal or regulatory standpoint whether CT scanners were cleared for screening of asymptomatic patients because they were not appropriate predicate devices for the Viatronix 510(k)s or other CT colonography devices. Accordingly, the absence of an indication

for asymptomatic screening for CT scanners does not invalidate the clearances for CT colonography devices for asymptomatic screening.

2. Allegation Concerning the Intended Use of the Viatronix Device

The whistleblower alleges that the 2004 change from diagnostic to screening use created a new intended use for the Viatronix device. To evaluate this issue, files for several devices were reviewed to determine what consideration was given contemporaneously to the question of whether the change from diagnostic to asymptomatic screening created a new intended use. The reviewed files were: (1) the Viatronix 510(k) for asymptomatic screening (K040126), (2) the predecessor Viatronix 510(k) for diagnostic use (K020658), and (3) CCI [redacted] In addition, agency documents reflecting the agency's interpretation and application of the concept of a "new intended use" at the time of the clearance of K040126 were reviewed. In light of this evidence, we considered whether the decision in K040126 not to treat the change in indication from diagnostic to asymptomatic screening violated or appeared to violate any law, rule, or regulation in place at the time of the clearance. We have concluded that it did not.

a. Contemporaneous Standards for Evaluating Intended Use

Under 21 U.S.C. § 360c(i), a new device may not be found substantially equivalent to a predicate device if the new device has a new intended use. A device with a new intended use must be reviewed under a PMA under 21 U.S.C. § 360e or if eligible, undergo a de novo review under 21 U.S.C. § 360c(f).

As the OIG noted, a change in a device's "indication for use" statement does not necessarily create a new intended use. 21 CFR 807.92(a)(5) describes the general standard a 510(k) submitter must meet to establish that a change in the indication for use is not a new intended use:

> If the indication statements are different from those of the legally marketed device identified [as a predicate device], the 510(k) summary shall contain an explanation as to why the differences are not critical to the intended therapeutic, diagnostic, prosthetic, or surgical use of the device, and why the differences do not affect the safety and effectiveness of the device when used as labeled.

In 1986, FDA issued agency guidance on the meaning of "substantial equivalence." This guidance was in effect in 2004 and throughout the period in which the allegations arose.[2] With

[2] Guidance on the CDRH Premarket Notification Review Program, 6/30/86 (K86-3), available online at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm081383.htm. An additional guidance 1998 document, "General/Specific Intended Use," which discussed a change from a general indication to a specific indication is not relevant here. According to that guidance document, diagnosis and screening are both specific indications with the same level of specificity.

respect to the meaning of "new intended use," the guidance provided a broad, discretionary standard for determining whether a change in indication for use created a new intended use, and provided general criteria for the determination:

> The Center's scientific expertise enables it to exercise considerable discretion in construing intended uses in the labeling and promotional materials for predicate and new devices. Thus, a new device with the same intended use as a predicate device may have different specific indication statements, and, as long as these label indications do not introduce questions about safety or effectiveness different from those that were posed by the predicate device's intended use, the new device may be found SE [substantially equivalent].
>
> For the purposes of determining whether or not the new device has the same intended use as a predicate device, the Center assesses any difference in label indications in terms of the safety and effectiveness questions they may raise. The Center considers such points as physiological purpose (e.g. removes water from blood, transports blood, cuts tissue), condition or disease to be treated or diagnosed, professional or lay use, parts of the body or types of tissue involved, frequency of use, etc.

The 1986 guidance also provided a substantial equivalence decision-making flowchart and explained that whether a new device has the same intended use as the predicate device "is normally based on descriptive information alone, but limited testing information is sometimes required."

Thus, in 2004, decisions on when a different indication for use created a new intended use were governed by the standards reflected in FDA regulation and guidance -- standards that allow for decision-making based on scientific expertise and judgment, sometimes aided by new clinical data.

b. Contemporaneous Scientific Decisions

To determine whether the 2004 decision violated existing laws, rules, or regulations, it is appropriate to look at how those FDA scientists involved in the review of the CT colonography devices contemporaneously evaluated the change in indication for use from diagnostic to asymptomatic screening.

(i) 2004 Viatronix Clearance

The principal medical reviewer for the Viatronix device, a radiologist, concluded that expanding the device's indication from diagnostic to asymptomatic screening did not call into question the device's safety and effectiveness and therefore was appropriate for clearance in a 510(k). He based his conclusion on Viatronix's submission of a large U.S. Government-funded clinical

study subsequently published in the New England Journal of Medicine.[3] The study was a blinded comparison of three-dimensional CT colonography to optical colonoscopy in the screening of over 1200 asymptomatic patients. The investigators found that CT colonography with the Viatronix device compared favorably with colonoscopy in detecting polyps and malignant lesions. The risks of the device described in the study were the risks of false negatives (sensitivity) and false positives (specificity). According to the published results the sensitivity of CT colonography was slightly better than that of colonoscopy, and the specificity was adequate though slightly less. Of two malignant polyps found among the study subjects, both were detected by CT colonography, but one was missed on optical colonoscopy.

The study also notes that in comparison to optical colonoscopy, CT colonography is non-invasive and does not require intravenous sedation, analgesia, or recovery time. The medical review of this study by the CDRH radiologist found the study adequate to support the change in indication:

> I have reviewed that paper, as well as an independent commentary on it, and have concluded that this study does indeed constitute an adequate demonstration of the safety and effectiveness of the company's software in screening an asymptomatic population to permit such usage to be included in their IFU [indication for use].

The conclusion that the there was an adequate scientific basis to find the Viatronix device substantially equivalent to the predicate device was accepted by the lead reviewer of the 510(k) and the Director of the Division of Reproductive, Abdominal and Radiological Devices, who cleared the 510(k) permitting the change in indication.

The standard for assessing new intended uses in place at the time of this decision was flexible and based on individual scientific judgments, and sometimes supported by clinical data. Given the reviewer's scientific conclusion that the large clinical study supported the safety and effectiveness of the device for asymptomatic screening, it was not inconsistent with existing standards for the Division to conclude that expansion in indication from diagnostic or asymptomatic screening was "not critical to the intended therapeutic, diagnostic, prosthetic, or surgical use of the device, and [that] the differences do not affect the safety and effectiveness of the device when used as labeled." 21 CFR § 807.92(a)(5).

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[3] Pickhardt PJ, Choi JR, Hwang I, et al, Computed Tomographic Virtual Colonoscopy to Screen for Colorectal Neoplasia in Asymptomatic Adults, *N Engl J Med* 2003;349: 2191-200; available online at: http://www.nejm.org/doi/full/10.1056/NEJMoa031618#t=article.

Accordingly, the decision that the change from a diagnostic to an asymptomatic screening indication did not constitute a new intended use does not appear to have violated any law, rule, or regulation in place at the time.

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Two medical reviewers argued that the change from diagnostic to asymptomatic screening created a new intended use, contending that the Viatronix device was never cleared to screen asymptomatic patients. The director of CDRH's Biophysics Laboratory, which among other things, studies imaging devices and safe levels of use in humans, was asked to conduct a review of the issues cited by the two reviewers. He disagreed with their arguments concerning intended use and concluded that the 2004 decision should not be invalidated. CDRH also conducted an evaluation of the risks and benefits of CT colonography devices in response to safety concerns raised by two reviewers. The evaluation included scientific reviews of the clinical study that supported clearance of the Viatronix device (showing that the device compared favorably with colonoscopy in screening asymptomatic patients) as well as evaluations of the available evidence on the radiation risks associated with CT colonography.

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c. Analogous Case

The Office of the Commissioner found that in a closely analogous case decided more recently, CDRH concluded that a change in indication from diagnostic to asymptomatic screening was not a new intended use. Software used to assist in displaying images from optical colonoscopes was cleared for a screening indication, citing a predicate software device whose indication for use did

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not include such screening.[5] As noted above, colonoscopes are not themselves indicated for asymptomatic screening. Thus, CDRH has found that the change from diagnostic to asymptomatic screening is not a new intended use consistently for both software used with CT scanners and software used with colonoscopes.[6]

d. New Draft Guidance

In December 2011, FDA issued new draft guidance on evaluating substantial equivalence.[7] The purpose of the draft guidance is to provide greater clarity with respect to FDA's review process for evaluating substantial equivalence and not intended to implement significant policy changes to the current review process. The draft guidance includes greater specificity about when a new indication for use may result in a new intended use. The draft guidance makes clear that the agency understands that changes from diagnostic to screening indications, among other types of changes in indication, "warrant particular attention" in evaluating whether they create a new intended use and are likely to affect safety or effectiveness. The complete list of these types of changes follows:

- A change from a functional/performance indication to a treatment or aesthetic indication;
- A change from a diagnostic indication to a screening indication, or vice versa;
- A change in the anatomical structure of use;
- A change in the patient population (e.g., adult versus pediatric; different disease populations);
- A change in the clinical context or setting (e.g., periodic monitoring versus continuous monitoring; hospital versus home use).

Obviously, not every indication change that might fall within one of these categories would result in a significant change in safety or effectiveness, nor would every change result in a new intended use. Nevertheless, the guidance reflects the agency's intention to make such changes cautiously and with a thorough review of potential changes in safety or effectiveness.

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[5] K102949 for the Colonoscopy Assistant software device. 510(k) Summary available at: http://www.accessdata.fda.gov/cdrh_docs/pdf10/K102949.pdf.

[6] Both colonoscopy and CT colonography are less likely to identify a serious disease in asymptomatic patients than in symptomatic patients. Thus, both have a smaller benefit for asymptomatic patients. At the same time, both procedures present potentially significant risks. The risks of colonoscopy include perforation of the bowel, major bleeding, and transmission of infectious diseases. To the extent that exposing asymptomatic patients to the risks of CT colonography and colonoscopy creates a somewhat different benefit/risk ratio than for symptomatic screening, it does so for both devices.

[7] Draft Guidance for Industry and Food and Drug Administration Staff – The 510(k) Program: Evaluating Substantial Equivalence in Premarket Notifications [510(k)], December 27, 2011; available online at: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm282958.htm. Neither draft nor final guidance documents are binding on the agency and do not have the force of law.

We have concluded that this draft guidance is consistent with the 2004 and 2009 decisions on CT colonography for asymptomatic screening. Most importantly, the record of CDRH's lengthy consideration of the intended use issue in the course of the review CCI shows that it gave precisely the careful scientific and regulatory attention to the issue recommended by the guidance. In the course of this review, CDRH concluded that rescission of the 510(k) for the Viatronix device was not appropriate. Second, the recent decision on the change from diagnostic to asymptomatic screening for colonoscopy software shows that CDRH has been consistent in finding that this type of change is not necessarily a new intended use.

e. Conclusion

We find that it was not contrary to any statute, regulation, or policy in place in 2004 and 2009 for CDRH to conclude that the change from a diagnostic to an asymptomatic screening indication for CT colonography did not create a "new intended use." We based this finding on: (1) the standards for determining whether a change in indication for use constitutes a "new intended use" as reflected in FDA regulation and guidance at the time the relevant decisions were made; (2) contemporaneous scientific decisions that the change in indication for use from diagnostic to asymptomatic screening did not create a new intended use; (3) evidence that analogous changes in indication statements for software used with colonoscopies were not considered changes in intended use; and (4) CDRH's thorough reconsideration of the legal and scientific bases for the clearance of Viatronix device in the course of the CCI.

D. Findings on the Allegations in Section II.B of the Referral Letter

> *Allegation: The clearance of K040126 was in error because the documentation in the administrative file was inadequate and violated 21 CFR § 10.70, FDA's regulation concerning documentation of agency decisions, because there was no signed review memorandum or similar documentation showing an analysis of the predicate device, aside from a brief statement from the reviewer that he read the report that was submitted by Viatronix.*

The OIG investigated this allegation and made findings concerning the documents in the administrative files for both Viatronix 510(k)s (K020658 and K040126).

The OIG described FDA's documentation of medical device approval and clearance as follows:

> FDA creates an administrative file for each device undergoing the PMA or 510(k) review process. The regulations require FDA to document in the administrative file "every significant FDA decision on any matter under the laws administered by the [FDA] Commissioner."[8]... FDA has not defined what constitutes a significant decision as it relates to the device approval or

[8] 21 CFR § 10.70(a)

> clearance processes. For the purposes of the review, the OIG considered the decisions to approve or clear the devices significant. FDA does not have procedures for documenting the significant decision to approve or clear a device. Further, FDA has not defined, beyond the requirements of 21 CFR § 10.70, the specific documents that must be in administrative files. FDA has not defined written documents that require signatures and dates.

We note that CDRH last week released a new Standard Operating Procedure (SOP) on compiling an administrative file for premarket submissions,[9] but this was not in the OIG's possession at the time of its review. In the absence of FDA regulations or policies concerning the documents that must be included in a 510(k) file, the OIG assessed what documents "should reasonably be included in an administrative file." It based its assessment on prior OIG reviews of 510(k) administrative files and input from FDA officials during previous work. Among the documents that the OIG concluded should reasonably be included in a 510(k) file is the reviewer's memorandum.

1. OIG Finding

With respect to the issue of whether there was a signed review memorandum or similar documentation showing an analysis of the predicate device, the OIG made the following findings:

> The 2004 file for the Viatronix device did not include one piece of documentation of the reviewer's analysis; the Reviewer Memorandum documenting the review of new evidence that resulted in the change to the Indications for Use was not in the file. The 2004 file for the Viatronix device updated the Indications for Use for the 2002 Viatronix device based on newly submitted scientific evidence. The 2004 file for the Viatronix device states that an FDA reviewer concluded that this evidence was adequate to clear the new Indications for Use. However, no memorandum documenting the review of this evidence is included in the 2004 file for the Viatronix device. We located this unsigned Reviewer Memorandum in the 2002 file for the Viatronix device.
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> Based on our review of the unsigned Review Memorandum found in the 2002 file for the Viatronix device, we determined that the sponsor submitted the evidence on November 17, 2003, to change the Indications for Use already cleared in the 2002 Viatronix submission. The FDA reviewer completed his review of the new evidence on December 4, 2003. In a letter dated December 9, 2003, FDA informed the sponsor that this evidence would support the change in the Indications for Use. In the December 9 letter, FDA

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[9] Copies of this SOP may be requested from Philip.Desjardins@fda.hhs.gov.

> invited the sponsor to submit a new 510(k) to formally change the Indications for Use and assured the sponsor that the submission would receive a rapid review. The sponsor then submitted the evidence in the form of a new 510(k) submission on January 15, 2004. The 510(k) submission for the new Indications for Use was cleared by FDA on April 19, 2004.

The OIG also found some other documentation in the file related to the reviewer's analysis was not signed or dated and that the FDA acknowledgement letter was not signed. However, the file included all other correspondence between FDA and the sponsor and other standard documents.

The OIG stated that missing or unsigned documents do not necessarily indicate that the devices were not appropriately cleared. The OIG did not attempt to reach a conclusion as to whether the devices were appropriately cleared.

2. Office of the Commissioner Review

Relying on these findings by the OIG, we considered whether: (1) the documentation of the clearance for K040126 violated 21 CFR § 10.70; and (2) the fact the review memorandum was missing from the file for K040126 invalidated the Viatronix device 510(k) clearance, such that it could not be a predicate for the subsequent CT colonography software devices for asymptomatic screening.

21 CFR § 10.70 requires, among other things, that FDA document in an administrative file "every significant FDA decision on any matter under the laws administered by the [FDA] Commissioner."[10] Documentation of a significant decision includes "[a]ppropriate documentation of the basis for the decision, including relevant evaluations, reviews, memoranda, letters, opinions of consultants, minutes of meetings, and other pertinent written documents, and [t]he recommendations and decisions of individual employees, including supervisory personnel, responsible for handling the matter."[11] Documents that are prepared by agency employees but are not in the administrative file have "no status or effect".[12] Finally, written documents in the administrative file must be signed and dated by the author.[13]

With respect to whether 21 CFR § 10.70 was violated, we concur with the OIG's finding that in 2004 there were no FDA rules in place detailing the specific documents that must be in a 510(k) file and therefore constituted "[a]ppropriate documentation of the basis for the decision, including relevant evaluations, reviews, memoranda, letters, opinions of consultants, minutes of meetings, and other pertinent written documents; and the recommendations and decisions of

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[10] 21 CFR § 10.70(a).
[11] 21 CFR § 10.70(b).
[12] 21 CFR § 10.70(d).
[13] 21 CFR § 10.70(e)(2).

individual employees, including supervisory personnel, responsible for handling the matter." Nevertheless, the OIG determined that a 510(k) file should reasonably include a copy of the reviewer's memorandum, and in this case, the reviewer's memorandum was filed in the 510(k) for the predecessor Viatronix device and was unsigned. In addition, some other documents lacked signatures and dates. We find that under these circumstances, the 510(k) file could be considered to not fully comply with 21 CFR § 10.70.

The probable violation of 21 CFR § 10.70 did not create a basis to invalidate K040126, however, as alleged by the whistleblower. A cleared 510(k) would be invalidated by the absence of the reviewer's memorandum or other unsigned or undated documents only if 21 CFR § 10.70 or other statutory or regulatory provisions related to 510(k) clearances expressly provided that such circumstances could constitute a basis for nullifying a 510(k).

Neither 21 CFR § 10.70 or other statutory or regulatory provisions related to 510(k) clearances provide a basis to invalidate K040126. Even a clear violation of 21 CFR § 10.70 would not by itself result in the invalidation of a 510(k) clearance decision. Section 10.70 does not carry any penalties, or otherwise specify any consequences that follow from a violation of the section. Nor do any of the statutory or regulatory provisions related to 510(k) clearances provide a basis for invalidating a clearance simply because the medical review is misfiled in another administrative file or otherwise adequate documents are unsigned or undated. *See* 21 USC § 360c(i); *see also* 21 CFR § 807.100.

The missing document existed and was filed in the administrative file for the prior 510(k) for the device, and a reference to the reviewer's conclusions was contained in K040126. The other documentation errors were minor. We find that the probable violation was not significant and did not call into question either the legal or scientific basis for clearing the 510(k). However, as noted above, CDRH has now released a set of SOPs for compiling the administrative file for premarket submissions. In addition, we will ask CDRH to correct the error created by the misfiling of the reviewer's memorandum by adding a copy to the administrative file for K040126 with a cover memo explaining the circumstances of its addition.

E. Findings on the Allegations in II.C of the Referral Letter

> *Allegation: The improper clearance of the devices led to their use on asymptomatic patients, potentially exposing millions of otherwise healthy people to unnecessary radiation and creating a significant increased cancer risk which, the whistleblower conservatively estimates, could result in an increase of approximately 7,000 cases of colon cancer per year.*

We have investigated this allegation and made findings and recommendations consistent with the regulatory framework created by Congress for approval and clearance of medical devices. First,

we reviewed evidence concerning the rates of colorectal cancer in the U.S., recommendations for universal colorectal screening over age 50, the low rates at which such screening is occurring, and the role of CT colonography in colorectal screening. Second, we have reviewed how CDRH evaluated the safety and effectiveness issues when they were first raised in 2009. Third, we have reviewed the state of outside expert views on the use of CT colonography for screening. Fourth, we have reviewed the claim that use of CT colonography for asymptomatic screening could result in an increase of 7,000 colon cancers per year. Finally, we have recommended a process for obtaining a formal expert review of this question that will inform FDA's continuing regulation of CT colonography devices. In the unique circumstances presented here, including the questions raised by the Office of Special Counsel about CT colonography as well as the evolving science and public discussion concerning its use for asymptomatic screening, we recommend that the Commissioner exercise her discretion, under 21 CFR §14.1(a)(1), to hold an advisory committee meeting to consider current data on the risks and benefits of these devices.

1. The Role of CT Colonography in Colorectal Screening

Colorectal cancer is the second leading cause of cancer deaths in the U.S. According to the Surveillance, Epidemiology and End Results program of the National Cancer Institute, it is estimated that 143,460 men and women (73,420 men and 70,040 women) will be diagnosed with and 51,690 men and women will die of colorectal cancer in 2012. About 1 in 20 Americans (5%) will be diagnosed with colorectal cancer at some point in their lifetimes.[14]

Early detection of colorectal cancer and removal of pre-cancerous lesions has been shown to improve survival. The five-year survival rate for colorectal cancers detected at an early, localized stage is 90%.[15] And colorectal cancer can be prevented from developing, if pre-cancerous polyps are detected and removed. Over half of those Americans who will die this year from colorectal cancer could have been saved by screening or early detection.[16] As a result, colorectal cancer screening is universally recommended for adults between 50 and 75. Despite the recommendation, and public health and Congressional attempts to encourage screening, only about 60% of Americans who meet the criteria for screening are screened.[17] And only 39% of cases are detected at an early stage.[18]

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[14] SEER Stat Fact Sheets: Colon and Rectum, National Cancer Institute, Bethesda, MD; available online at http://seer.cancer.gov/statfacts/html/colorect.html.

[15] American Cancer Society. Cancer Facts & Figures 2012. Atlanta, GA: American Cancer Society; 2012.

[16] Colditz G, Atwood K, Emmons K, et al, For the Risk Index Working Group, Harvard Center for Cancer Prevention. Harvard Report on Cancer Prevention Volume 4: Harvard Cancer Risk Index. Cancer Causes Control. 2000; 11(6):477-488.

[17] Behavioral Risk Factor Surveillance System 2010, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, 2011.

[18] American Cancer Society. Cancer Facts & Figures 2012. Atlanta, GA: American Cancer Society; 2012.

There are a number of reasons for the low screening rates. One is that many patients are reluctant to undergo optical colonoscopy, the most accepted method of colorectal cancer screening, due to the discomfort of the procedure and inconvenience of the required bowel preparation.[19]

There are several types of screening methods. Some methods, such as the fecal occult blood test, primarily detect already-developed cancer. Others, such as colonoscopy, sigmoidoscopy, and CT colonography, can also detect pre-cancerous polyps. The latter type has a greater capability to prevent cancer and improve survival.

Of the methods that can detect both cancer and precancerous polyps, there are differences in risks, benefits, and patient acceptance. According to the Joint Guideline from the American Cancer Society, the US Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology (Joint Guideline), which evaluated and recommended several methods, including CT colonography:

> No CRC [colorectal cancer] screening test is perfect, either for cancer detection or adenoma [a kind of polyp] detection. Each test has unique advantages, each has been shown to be cost-effective, and each has associated limitations and risks.[20]

For example, colonoscopy and sigmoidoscopy are the only methods that can both detect polyps and remove them at the same time. Colonoscopy has a high rate of sensitivity and specificity for the entire colon. On the other hand, colonoscopy has a higher risk of bowel perforation than some methods (estimated at 1/500 for Medicare-age patients and 1/1000 overall[21]) and requires sedation to minimize discomfort, which poses its own risks. According to the Joint Guideline, "complications related to CSPY [colonoscopy] are a significant public health challenge."

CT colonography is non-invasive and does not require sedation, pain control, or recovery time, but poses a risk from the radiation used to make the images. Otherwise, it has few side effects. The radiation dose used is being steadily reduced, to a fraction of the dose used when the technology was introduced; nevertheless, there is a risk of induced cancers. Increasingly, studies find CT colonography to have a high rate of sensitivity and an acceptable rate of specificity for

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[19] Berrington de Gonzalez A, Kim KP, Yee J. CT colonography: perforation rates and potential radiation risks, Gastrointest Endosc Clin N Am 2010;20(2): 279-91; available online at http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2956272/.

[20] Levin B, Lieberman DA, McFarland B, et al. Screening and surveillance for the early detection of colorectal cancer and adenomatous polyps, 2008: a joint guideline from the American Cancer Society, the US Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology. *CA Cancer J Clin* 2008;58:130-160; *Gastroenterology* 2008; 134:1570-1595; available online at: http://www.gastrojournal.org/article/S0016-5085(08)00232-1/fulltext ; *Radiology* 2008;248:717-720.

[21] Gatto NM, Frucht H, Sundararajan V, Jacobson JS, Grann VR, Neugut AI, Risk of perforation after colonoscopy and sigmoidoscopy: a population-based study, *J Natl Cancer Inst* 2003;95:230-236; available online at: http://jnci.oxfordjournals.org/content/95/3/230.full.

the most important types of polyps. It is less able to detect very small polyps, although the clinical significance of these is less certain. CT colonography also requires follow-up colonoscopy to remove suspicious polyps that are detected. Finally, CT colonography may produce "extra-colonic" findings, i.e., potentially serious findings in surrounding organs or tissues. These findings have both benefits (the detection of serious illnesses) and risks (false positives which nevertheless require further testing).

Other accepted technologies, such as flexible sigmoidoscopy and barium contrast enema, also have advantages and disadvantages. Flexible sigmoidoscopy requires somewhat less bowel preparation than colonoscopy and colonography but cannot detect lesions in the roughly two-thirds of the colon it cannot reach and can be quite uncomfortable for the patient. Double-contrast barium enemas can visualize the entire colon, but also deliver a radiation dose comparable to CT colonography or higher.[22] Like CT colonography, double-contrast barium enemas require follow-up colonoscopy if polyps are detected.

Because of the relatively low acceptance rate of colonoscopy, having available other safe and effective screening options is an important public health goal. No single screening option is optimal for all patients. Many hope that because CT colonography is non-invasive and does not require sedation, it will be more acceptable to individuals who would not otherwise be screened, increasing the total number of individuals who undergo screening. Some studies suggest that the availability of CT colonography does increase the number of patients who are willing to undergo screening.[23] In addition, it is an important tool for screening patients who cannot tolerate colonoscopy or who have had a failed colonoscopy.[24]

2. CDRH's 2009 Review

In 2009, when two medical reviewers argued that the radiation risk from CT colonography outweighed its benefits, CDRH addressed these concerns carefully and thoroughly. In addition to lengthy internal debates within the reviewing division concerning the radiation risk, CDRH

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[22] Neri E, Faggioni L, Cerri F, et al, CT colonography versus double-contrast barium enema for screening of colorectal cancer: comparison of radiation burden, *Abdom Imaging* 2010;35(5):596-601.

[23] Pooler BD, Baumel MJ, Cash BD, et al, Screening CT Colonography: Multicenter Survey of Patient Experience, Preference, and Potential Impact on Adherence, *Amer J Roentgenology*, 2012;198(6):1361-1366; available online at http://www.ajronline.org/content/198/6/1361.long; Wijkerslooth TR, de Haan MC, Stoop EM, et al, Burden of colonoscopy compared to non-cathartic CT-colonography in a colorectal cancer screening programme: randomized controlled trial, *Gut* 2011; [cite?] http://gut.bmj.com/content/early/2011/12/22/gutjnl-2011-301308.abstract; Gluecker TM, Johnson CD, Harmsen WS, et al Colorectal cancer screening with CT colonography, colonoscopy, and double-contrast barium enema examination: prospective assessment of patient perceptions and preferences, *Radiology* 2003;227(2):378-84; available online at: http://radiology.rsna.org/content/227/2/378.long.

[24] Levin B, Lieberman DA, McFarland B, et al. Screening and surveillance for the early detection of colorectal cancer and adenomatous polyps, 2008: a joint guideline from the American Cancer Society, the US Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology. *CA Cancer J Clin* 2008;58:130-160; *Gastroenterology* 2008;134:1570-1595; available online at: http://www.gastrojournal.org/article/S0016-5085(08)00232-1/fulltext; *Radiology* 2008;248:717-720.

undertook a formal review of the available evidence relating to the effectiveness of CT colonography for colorectal screening, and assessed the risk to patients from radiation exposure. This review was carried out by the OSB, which is a separate office from the offices that carry out device approval. Its function is to conduct assessments of the benefits and risks of medical devices and radiological products using state-of-the-art statistical, epidemiological, and surveillance methods. OSB provided a comprehensive and detailed report on CT colonography screening, including: (1) a review of all published clinical data on the effectiveness of the CT colonography compared to colonoscopy for screening; (2) an assessment of the radiation risk associated with CT colonography; and (3) a comparative assessment of the risks of perforation, hemorrhage, and infectious disease transmission in colonoscopy and CT colonography.

OSB found that colon cancer is one of the most important forms of cancer, as it is the third most common cancer and the second greatest cause of mortality from cancer in the United States. OSB further found that (1) the vast majority of colon cancers arise from colonic polyps; (2) the timely detection and removal of colonic polyps can prevent the development of colon cancer; (3) the value of secondary prevention for colon cancer is heightened by the particularly poor prognosis of metastatic colon cancer; and (4) patients with metastatic spread of colon cancer to other organs, such as the liver, have a 5 year survival rate of less than 10%.

OSB's evaluation concluded that the medical and scientific literature provided "compelling evidence" of the clinical utility of screening for colonic polyps with CT colonography, particularly because patients' acceptance of the CT colonography procedure is much higher than that of colonoscopy, potentially increasing the total number of individuals screened and cancers detected early. With respect to radiation risk, OSB concluded that the risk is small but not zero. Using a model known as "linear no threshold," OSB found that at age 50, the estimated risk of inducing a cancer from the radiation exposure from 1 colonography examination is 1 in 700. This risk falls substantially with advancing age to 1 in 1,400 at age 70.[25] Note that these are cancers, not cancer deaths. With respect to the comparative risks of colonography and colonoscopy, OSB found that the risk of perforation was rare for both, but significantly higher in colonoscopy than CT colonography. Major bleeding and infectious disease transmission from inadequately disinfected colonoscopes were also found to be rare but potentially life-threatening risks for colonoscopy, but not CT colonography.

OSB found that the benefits of the CT colonography for screening were substantial and that they outweighed the small radiation risk. OSB concluded:

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[25] The OSB reviewers noted that there is some dispute about whether the linear no threshold model is correct, and that other models predict a lower radiation risk. Another CDRH reviewer pointed to conclusions of some radiation experts and the Health Physics Society, a scientific, professional organization, that, at radiation doses below 50-100mSv, the human health effects are either too small to be observed or are nonexistent. This dose is significantly higher than the dose received from CT colonography, which is between 5 and 13mSv, and is being reduced over time.

> Justification is a vital principle of radiation protection. This principle mandates that patients not be exposed to ionizing radiation without adequate benefit. It is the unanimous view of this review team that the radiation exposure from virtual colonoscopy is justified. The very high levels of sensitivity and specificity for colonic polyp detection, coupled with the high incidence of colon cancer, extremely poor prognosis of metastatic colon cancer, and the fact that the timely detection and removal of colonic polyps can prevent colon cancer all combine to strongly support the contention that screening with virtual colonoscopy will provide very considerable benefits to screened patients. We believe the benefit risk ratio for this procedure is highly favorable. Finally, we would note that the risk component of the equation is not fixed. The radiation dose from the procedure can be reduced through measures such as the optimization of the scan parameters. Reducing the radiation exposure will reduce the radiation risk. Such measures are highly consistent with the ALARA (As Low As Reasonably Achievable) principle and are worthy of concerted Center support.

In 2010, CDRH launched its "Initiative to Reduce Unnecessary Radiation Exposure from Medical Imaging," including CT scans.[26] The purpose of the initiative is to ensure that each patient receives only those imaging exams that are medically necessary, and that they receive the lowest possible radiation dose. CDRH is pursuing these goals through facility guidelines and personnel qualifications, education and communication, appropriate use, equipment safety features, tracking radiation safety metrics, and research on radiation dose optimization.

Thus, in 2009, at the time the whistleblower first made these allegations, CDRH undertook a careful review of the scientific data and concluded that benefits of CT colonography outweighed its risks as an option for screening asymptomatic individuals. CDRH also embarked on a major initiative to ensure that the radiation doses associated with medical imaging are as low as possible, and that physicians and patients are informed about radiation risks and how to reduce them. CDRH is working with manufacturers to develop CT scanners and software that provide smaller doses of radiation and some of these are already on the market. CDRH is also developing dose reference standards for the minimum radiation dose necessary to generate images of sufficient quality for accurate diagnosis or screening.

3. Published Views of Outside Experts

The whistleblower points to the 2009 Centers for Medicare & Medicaid Services (CMS) decision not to expand coverage under part B for Medicare patients for CT colonography screening as evidence that current research does not support its use. The whistleblower is correct that CMS reached a different conclusion than CDRH, but the question before CMS was different in important ways from the regulatory question before FDA. Among other things, given the

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[26] Initiative to Reduce Unnecessary Radiation Exposure from Medical Imaging, available on line at http://www.fda.gov/Radiation-EmittingProducts/RadiationSafety/RadiationDoseReduction/default.htm.

existing coverage of alternative colorectal cancer screening tests, CMS was seeking evidence specifically on the performance of CT colonography in patients 65 years and older (the Medicare population), which it concluded was insufficient.[27] For example, in observing that other health plans and insurers do reimburse for CT colonography screening, CMS said:

> From the Medicare perspective, it is also important to emphasize that the populations served by other health plans and insurers are significantly younger than the Medicare population, and thus would likely have a lower prevalence of polyps, lower test positive rates and lower rates of referral for optical colonoscopy with polypectomy. In these younger populations, the results from the studies by Pickhardt (2003), Kim (2007) and Johnson (2008) [finding that CT colonography is comparable to colonoscopy] would be more directly applicable. Unfortunately, the currently available evidence is not generalizable to the Medicare population.

In addition, the CMS decision took into account other appropriate factors including issues that are not relevant to FDA's statutory assessment in evaluating substantial equivalence.

Many medical groups and insurers have, however, reached conclusions that were consistent with CDRH's. For example, in 2008, the American Cancer Society, the US Multi-Society Task Force on Colorectal Cancer (which represents the American Gastroenterological Association (AGA), the American Society for Gastrointestinal Endoscopy, and the American College of Gastroenterology), and the American College of Radiology issued a joint guideline on colon cancer screening. That guideline concluded that there were now sufficient data to include CT colonography as an acceptable option for colon cancer screening.[28] Some large health plans and private insurers, including Kaiser Permanente and Blue Cross/Blue Shield, have also carried out reviews and concluded that the benefits of CT colonography for screening outweigh its risks.[29]

At the same time, some organizations have concluded that there is still insufficient information to support CT colonography for screening of asymptomatic patients. These include the California

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[27] CMS, Decision Memo for Screening Computed Tomography Colonography (CTC) for Colorectal Cancer (CAG-00396N), May 12, 2009; available online at: http://www.cms.gov/medicare-coverage-database/details/nca-decision-memo.aspx?NCAId=220&NcaName=Screening+Computed+Tomography+Colonography+(CTC)+for+Colorectal+Cancer&TAId=58&IsPopup=y&bc=AAAAAAAAIAAA&.

[28] Levin B, Lieberman DA, McFarland B, et al. Screening and surveillance for the early detection of colorectal cancer and adenomatous polyps, 2008: a joint guideline from the American Cancer Society, the US Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology. *CA Cancer J Clin* 2008;58:130-160; *Gastroenterology* 2008; 134:1570-1595; available online at: http://www.gastrojournal.org/article/S0016-5085(08)00232-1/fulltext; *Radiology* 2008;248:717-720.

[29] Technology Evaluation Center, Blue Cross Blue Shield Ass'n, CT Colonography ("Virtual Colonoscopy") for Colon Cancer Screening, Aug. 2009; available online at http://www.bcbs.com/blueresources/tec/vols/24/24_01.pdf.

Technology Assessment Forum, the US Preventive Services Task Force,[30] and America's Health Insurance Plans.

Most of these evaluations of CT colonography for screening, like CDRH's, are 3-4 years old. In 2011, the AGA issued an update on its standards for performing and interpreting CT colonography, including screening of asymptomatic patients, based on new information since its 2007 standards were issued.[31] The review of evidence included new studies published since 2009, when the last of the reviews noted above was issued. The AGA Task Force found that there are new published studies on the use of CT colonography screening in Medicare-eligible patients ($\geq$ 65 years old), and that it now "appears that results obtained with CT colonography in the Medicare-eligible population are similar to those observed in general screening populations."

4. Allegation Concerning Potential Increase in Colon Cancers

We have found no significant basis for the whistleblower's estimate that the availability of CT colonography as an option for screening of asymptomatic patients could result in an increase of 7,000 colon cancers per year in either the data available from the CDRH reviews of these devices or in the published literature. The assumptions underlying this estimate are not stated, and no scientific evidence has been presented to support the assertion, so it is difficult to assess or respond to.

Nevertheless, it does not appear to be based on a fair assessment of relevant factors. For example, it appears likely that the estimate does not take into account the number of colon cancers that would be prevented by the early detection of pre-cancerous polyps through CT colonography. To our knowledge, none of the outside scientists or groups who have studied or reviewed CT colonography, including those who have expressed concern about the radiation risk, have suggested that the technology would result in a net increase in the number of colon (or other) cancers. A recent risk-benefit analysis directly compared the risks of radiation-induced cancers against the benefits of preventing cancers using CTC. In various microsimulation models, assuming screening every five years from age 50-80, CT colonography prevented between 24 and 35 times as many colorectal cancers as total cancers induced by radiation. The authors state that the benefits of screening using CTC under these circumstances "clearly

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[30] US Preventive Services Task Force (USPTF). Screening for colorectal cancer; U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med.* 2008:149:627-637; The Guide to Clinical Preventive Services 2010-2011 recommendations of the US preventive services task force; available online at http://www.ahrq.gov/clinic/pocketgd1011/pocketgd1011.pdf.

[31] AGA Standards for Gastroenterologists for Performing and Interpreting Diagnostic Computed Tomography Colonography: 2011 Update, *Gastroenterology* 2011;141:2240-2266; available online at http://www.gastrojournal.org/article/S0016-5085(11)01368-0/fulltext.

outweigh the radiation risks."[32] To our knowledge, none of the outside scientists or groups who have studied or reviewed CT colonography, including those who have expressed concern about the radiation risk, have suggested that the technology would result in a net increase in the number of colon (or other) cancers.

To obtain a reasonable estimate of the impact of CT colonography on public health, including impact on cancer rates, one would have to take into account the benefits and risks of CT colonography as well as those of alternative methods of colorectal screening. Factors could include: (1) the effectiveness of CT colonography and alternative methods of screening in detecting cancerous and pre-cancerous lesions, (2) the rate at which CT colonography would be expected to substitute for or augment those methods in the population for whom screening is recommended, (3) the fraction of patients who would require a follow-up colonoscopy to remove detected polyps, (4) a comparison of the immediate complication rates of CT colonography and colonoscopy, (5) the impact of extra-colonic findings from CT colonography (both positive and negative effects), (6) an estimate of cancers caused by CT colonography, which is in turn dependent on the dose administered (and which appears to be diminishing over time), and (7) the rate at which pre-cancerous lesions progress to cancer, and the related mortality rate. It is not possible to determine which of these factors or others the whistleblower's estimate takes into account, but it appears unlikely that the estimate is based on a full analysis of relevant factors.

III. Allegations Related to Digital Mammography Device

A. Regulatory History

1. Regulation of Digital Mammography

Full-field digital mammography (FFDM) is a breast-imaging modality where traditional x-ray screen-film is replaced by a digital image receptor. Digital mammography produces computerized x-ray images of the breast, rather than film x-ray images.

The first digital mammography device was approved in 2000. Until November 4, 2010, digital mammography devices were classified in Class III, because they were then considered novel systems for screening and diagnosing breast cancer. Class III provides the highest level of regulatory control of devices, and most Class III devices must go through the most stringent premarket approval process, the PMA process. In 2005, results of the ACRIN Digital Mammographic Imaging Screening Trial (DMIST), one of the largest breast cancer screening studies ever performed, were published and showed no difference between digital and film

[32] Berrington de Gonzalez A, Kim KP, Knudsen AB, et al. Radiation-Related Cancer Risks from CT Colonography Screening: A Risk-Benefit Analysis, Amer J of Roentgenology, 2011;196:816-823; available online at http://www.ajronline.org/content/196/4/816.long.

mammography in detecting breast cancer for the general population of women.[33] The study also showed that digital mammography detected significantly more cancers than screen film mammography in women 50 years old and younger, premenopausal women, and women with dense breasts. In 2006 and again in 2009, a panel of the Medical Device Advisory Committee unanimously recommended reclassifying digital mammography devices from Class III into Class II, under which new digital mammography devices would be cleared under 510(k)s rather than PMAs. In November 2010, FDA reclassified digital mammography devices into Class II because the technology had by that time been well-validated, and the benefits and risks of using digital mammography versus screen-film x-rays had been well-characterized.

2. Chronology of CDRH Review of the Carestream Digital Mammography Device

The Carestream Kodak DirectView Computed Radiography (CR) Mammography System (the Carestream device) is used in conjunction with the Kodak DirectView CR System and a conventional mammography x-ray machine to permit visualization and analysis of mammography images using digital (instead of screen-film) technology in the screening and diagnosis of breast cancer. It was reviewed as PMA P080018 and approved on November 3, 2010. It was the sixth and final FFDM device approved through the PMA process before the digital mammography devices were down-classified. However, its approval history is long and complicated. We review that history briefly here in order to give a sense of the depth of its review at CDRH, based on inspection of the full administrative record.

The DirectView CR Mammography System ("the Carestream device") was initially submitted as a PMA on December 30, 2005 (P060032). Evidently, the two studies submitted by Carestream met their pre-specified endpoints, but a variety of aspects of the tumors were deemed by FDA to not be representative of the general U.S. population and FDA, in a Not Approvable Letter on February 7, 2007, requested a new study to address these concerns. Realizing it would not meet the deadline for generating these data, Carestream withdrew its PMA on March 31, 2008.

FDA received P080018 on July 28, 2008 and it included additional clinical data to address the deficiencies identified in the Not Approvable Letter for P060032. The non-clinical data were reviewed in P060032 and are not reviewed here. The clinical study was a multi-center, prospective study in the U.S. and Canada in which 431 patients' mammograms were taken twice, once by the Carestream device and once by screen-film. In the primary analysis of these data, called the Enriched Reader Study (ERS), the Receiver Operating Characteristics (ROC) curve, sensitivity, specificity (all primary endpoints) and recall rate (secondary endpoint) of digital images and screen-film were compared. A second, subjective analysis, derived from the same data set and called the Comparative Feature Analysis (CFA), measured the subjective preferences of clinicians in the study for either the images produced by the Carestream device or those produced by screen-film. Fifty cases of confirmed cancer and 5 benign cases were rated on

[33] Pisano, ED et al, Diagnostic Performance of Digital versus Film Mammography for Breast-Cancer Screening, N Engl J Med 2005; 353:1773-1783, available online at: http://www.nejm.org/doi/full/10.1056/NEJMoa052911.

a 9-point Likert Scale (-4 (screen-film markedly better) to +4 (digital images markedly better)) with respect to a number of factors important to image quality, including the conspicuity or degree of visibility of various radiographic characteristics.

For the ERS, all endpoints were analyzed in a non-inferiority design in which the values of all outcomes for the digital images could be no more than 10% worse than ("non-inferior" to) screen-film. The study met those endpoints, i.e., showed that the digital images were comparable to screen-film in its ability to detect relevant lesions. For the CFA, however, a clinical reviewer noted that, although the lesion to be evaluated in the digital images and screen-film was clearly marked, reviewers were also permitted, at their own discretion, to compare other "relevant findings." The methodology for these relevant findings was not established, reviewers identified different relevant findings, and the relevant findings actually outnumbered the marked findings. In a November 24, 2008 Major Deficiency Letter, the sponsor was requested to address this problem by restricting the analysis in the CFA to only the marked findings and by including more benign cases. An additional two major deficiencies were identified in this letter, as well as a minor deficiency, but as these were successfully addressed by the sponsor in its subsequent submission, they are not described here.

On January 1, 2009, the sponsor responded with a subanalysis that presented the Likert Scale preferences of each reader for digital images and screen-film with respect to the nine mammogram features in the CFA, including conspicuity of masses, of architectural distortion and of microcalcifications. Of greatest interest to the reviewers was the finding related to conspicuity of microcalcifications, in which a trend toward a preference for screen-film over digital images was detected. This analysis was intended by the sponsor to be descriptive, and not to be subjected to statistical analysis.

On April 9, 2009, FDA issued a Not Approvable Letter, characterizing the conspicuity finding related to microcalcifications in the CFA as "strong" and noting that any new CFA "must be statistically significant, prospectively defined, and will need to be representative of a normal screening population in the United States."

On August 25, 2009, Carestream met with FDA in an informal "Request for Reconsideration." According to minutes from that meeting, FDA indicated that data already used in the CFA could be reanalyzed and that "New data would not need to be collected." The Not Approvable decision was ultimately upheld.

On September 24, 2009, the company submitted its response to the April 9, 2009 Not Approvable letter, including a post-hoc analysis of the existing data, restricted to the clearly marked cases. The company stated that this analysis confirmed that digital images were non-inferior to screen-film for the full dataset because the average score for digital images was not more than one Likert Scale point below screen-film. The lead reviewer, in a memo dated April 7, 2010, observed that for the subset of the data consisting of microcalcifications alone, digital

images were not non-inferior (three of four analyses showed differences in favor of screen-film of more than one Likert Scale point), although he acknowledged that "the sample size [25 cancers and 21 benign cases] is so small as to be difficult to interpret." In that same memo, he recommended issuing a second Not Approvable letter in which the company would be given the opportunity to address the microcalcification issue by obtaining additional cases.

On April 9, 2010, the Deputy Director for the Office of In Vitro Diagnostic Device Evaluation and Safety (OIVD), wrote to the lead reviewer saying that "I am not comfortable with your approach" and requesting review of the file by two mammography experts. Both mammography experts were from CDRH's Division of Mammography Quality Standards. Until that time, the review team had not included a radiologist with a specialty in mammography. One of their reviews stated that "the clinical significance of [the post-hoc analysis] is unclear" and that "there doesn't appear to be a substantive difference in the data submitted by Carestream compared with already approved units" from other manufacturers, i.e., the safety and effectiveness results for the Carestream device were comparable to those of other digital mammography systems that FDA had previously approved. The reviewer recommended that the issue be presented to the radiological advisory panel.

The more senior of the two mammographers was the Director of the Division of Mammography Quality Standards. Her review stated that, because mammographic lesions are combinations of masses, architectural distortion and microcalcifications, it is overall conspicuity that is the most important finding from the CFA, not the conspicuity of any subset of lesions such as microcalcifications. The "slight trend" of preference for screen-film for microcalcifications had been seen in other digital mammography systems and "[t]he question is whether that trend is clinically significant." The senior mammographer also disagreed that a "minimal to mildly better preference for screen-film over Carestream for one set of lesions" meant that the company had not documented reasonable assurance of safety and effectiveness. She said that just because one had a preference for the way the images appear on one machine did not mean that one could not make a diagnosis using a machine that was not one's preference.

After considering her review, and input from the 2009 advisory committee panel meeting on the reclassification of digital mammography devices, at which the panel did not recommend that FDA require CFAs for future clearances of these devices, a decision was made that a new panel meeting on this issue was not warranted.

At an internal meeting on June 2, reviewers discussed obtaining additional images from Carestream. On June 18, 2010, FDA requested that Carestream provide FDA with images from six patients, some of whom had microcalcifications. Two reviewers believed that the images from six patients were inadequate to resolve their concerns about the preferences of some reviewers in the clinical study for screen-film over digital images for microcalcifications.

The more senior mammographer reviewed the mammogram images, which contained microcalcifications, and pronounced them of "final interpretive quality." "Final interpretive quality" is a term of art equivalent to "can be used in the clinical practice of mammography." Under the Mammography Quality Standards Act, such images are those that are of high enough quality to be used to issue the final mammography report. The senior mammographer said that as long as microcalcifications were present and these were adequately visualized, it was not relevant if the microcalcifications were present in malignant or benign cases, an issue raised by some reviewers. The conspicuity of a microcalcification itself would not depend on whether it was benign or malignant. She recommended that the device be approved.

On July 23, 2010, a meeting including the Deputy Director, the lead reviewer, and the two mammography experts took place. Initially, the lead reviewer indicated that the application was non-approvable, based on the trend in the CFA toward a preference for screen-film for detecting microcalcifications. The Deputy Director indicated that the statistician and the mammography experts had concluded that the device was safe and effective, differing from the lead reviewer's recommendations. According to the meeting minutes, after the statistician and expert mammographers stated their views, the lead reviewer "said that there are new issues that the discussion brought to light ... he now feels comfortable with the microcalcification issue."

On August 16, 2010, the lead reviewer issued an Approvable recommendation. He reviewed the recommendations of the statistician and the two mammography experts and concluded, "Based on their recommendations for approval, the device should be found approvable." The Deputy Director concurred and an Approval Letter was sent to the sponsor on November 3, 2010.

B. Specific Whistleblower Allegations

The whistleblower alleges that the review of this PMA circumvented review and approval procedures and that CDRH approved the PMA despite concerns repeatedly raised by the review team 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 alleges further that the use of the device in breast cancer screening may lead to a significant increase in the misdiagnoses of, or failure to diagnose, breast cancer manifested as microcalcifications.

1. Allegations Concerning Safety and Effectiveness of the Carestream Device

The whistleblower alleges that conspicuity scores for microcalcifications in the CFA show that the Carestream device may be less able to detect malignant microcalcifications than SF, and that the ability of the device to detect malignant microcalcifications as well as SF could be assessed only by a further review of mammograms with malignant microcalcifications, which was not done. Ultimately, this entire issue revolves around the significance of the conspicuity scores for microcalcifications in the CFA.

a. Assessment

These concerns must be placed in perspective, taking the overall PMA application into account. This file clearly documents a lengthy and thorough review in which multiple viewpoints were heard and given a fair hearing. An initial PMA was rejected and a subsequent PMA was the subject of a Major Deficiency Letter, a Not Approvable Letter, a Request for Consideration, and requests for more analyses or images. Additional clinical reviewers with particular experience in mammography were engaged to clarify the significance of concerns raised in the review process. In addition, the following considerations demonstrate that the conspicuity of the microcalcifications in the CFA does not call into question the safety and effectiveness of the Carestream device:

(i) The primary study of the safety and effectiveness of the Carestream device, the ERS, met its predefined endpoints. In that study, the Carestream device was non-inferior to screen-film in sensitivity (false negatives) and specificity (false positives) for all outcomes, showing that the device was as effective as SF in detecting all relevant features.

(ii) Within the CFA, a subjective analysis, concern was raised only about the conspicuity of microcalcification issue, and not about conspicuity of masses and architectural distortion, or any of the six image quality analyses that also constitute the CFA.

(iii) The data on microcalcification conspicuity related to whether the study readers preferred digital images to screen-film, not to whether microcalcifications could be more readily detected by digital images or screen-film (this was addressed in the ERS); as a consequence the clinical significance of this finding is unclear.

(iv) While the number of images reviewed by one of the mammography experts in response to the concern raised by some reviewers about the CFA results was undeniably small, they do provide some overall clinical reassurance as to the clinical utility of the images. Given the issues enumerated in (i)-(iii) above, the Approvable Letter could appropriately have been issued even if the data to address the slight preference trend for screen-film over the Carestream device for microcalcifications had not been included in the data supporting the PMA.

b. Conclusion

We conclude that the approval decision was appropriate. It was based on a thorough review of all relevant data. The concerns of all members of the review team were given ample hearing and those concerns were appropriately responded to. The specific clinical data the whistleblower points to as evidence that the Carestream device was less able to detect malignant calcifications than screen-film were in fact of no clear clinical significance and were highly subjective. The data in question showed, at most, that the reviewers in the study may have preferred to look at

microcalcifications on screen-film rather than digital images, not that screen-film was better able to detect microcalcifications. Even this preference was confined to only one of nine elements in the more subjective analysis, the CFA. The actual sensitivity and specificity of the device for detecting malignancies in microcalcifications were adequately addressed in the more robust primary study analysis and showed comparability of CR to SF. Thus, the additional data sought by the whistleblower were unnecessary for a determination about the safety and effectiveness of the device.

Because the sensitivity and specificity of the device were comparable to screen-film, we also conclude that there is no reason to believe that use of the Carestream device will lead to a significant decrease in the rate at which breast cancers manifested as microcalcifications are diagnosed.

2. Allegations Concerning Procedural Violations

The whistleblower alleges that there were three procedural violations related to this review:

> (i) It was a violation of "FDA regulations governing the proper approval process" for the Deputy Director of the OIVD to seek expert consults on a review issue, and for those experts to be managers from another division outside ODE who had not been device reviewers;
>
> (ii) The Deputy Director's request that Carestream submit images from six patients who did not have cancer to address the microcalcification issue violated FDA regulations by "circumventing the April Not Approvable letter in the absence of any appeal or other legitimate reason"; and
>
> (iii) The Deputy Director failed to memorialize his actions described in (2) by placing documentation in the administrative file, in violation 21 CFR § 10.70.

a. Request for Expert Consult

The whistleblower does not cite a regulation governing the approval process that might have been violated by the Deputy Director's decision to seek expert consultation from experts outside the Office who had not previously been employed as reviewers. FDA's regulations on PMA review and approval are found at 21 CFR Part 814. There are no regulations in that Part or elsewhere governing whether anyone outside the review team may request an expert consultation on a PMA, or on whether consulted experts must be within the reviewing division, or have had prior employment as FDA reviewers. In this case, two facts make the Deputy Director's actions plainly consistent with sound review practice. First, the Deputy Director is a line supervisor of the review team. Second, CDRH has a separate division, staffed by experts in mammography, whose function is to oversee mammography quality standards across the nation (the Division of Mammography Quality and Radiation Programs). To suggest that the Office that reviews PMAs for mammography devices should not be allowed to call on those mammography experts in

another division in appropriate cases would undercut the effectiveness of FDA's oversight of mammography devices. The actions of the Deputy Director appear to have been a reasonable and responsible attempt to bring in mammography experts who were highly qualified in the specific technology before the agency, in order to assist in the resolution of a long-standing internal debate. We find that his actions do not violate or appear to violate any law, rule or regulation.

b. The April 2009 Not Approvable Letter

The Not Approvable letter in question, dated April 9, 2009, sought additional information on the conspicuity finding related to microcalcifications, in the form of a new CFA. On August 25, Carestream met with FDA in an informal "Request for Reconsideration." At that time, the record reflects that FDA told Carestream that data already used in the CFA could be reanalyzed and that "New data would not need to be collected." Carestream submitted a reanalysis of the data in September. After several more months of internal reviews, in April 2010, the Deputy Director requested review of the data by the two mammography experts. One of the experts disputed that a minimal to mild "preference" for screen-film rather than digital images by study reviewers meant that the Carestream device had not been shown to be safe and effective. An email from the lead reviewer to the review team states that an internal meeting on June 2, the team discussed obtaining additional images from Carestream. An email from one of the mammographers on June 16, 2010 to the review team, asks for an update on whether they had obtained the images discussed at the meeting. On June 18, 2010, the Deputy Director and the lead reviewer telephoned Carestream and requested that they submit six additional images with benign examinations. These were reviewed by the mammography expert, who recommended that the device be approved.

The whistleblower alleges that this action of the Deputy Director circumvented the April 2009 Not Approvable letter in the absence of an appeal or other legitimate reason. In light of the meeting with Carestream following the Not Approvable letter at which FDA agreed that Carestream did not have to perform a new CFA and could submit a reanalysis of existing data, as well as the apparent internal agreement that he should seek additional images from Carestream, we do not find the Deputy Director's June 2010 request for additional data to be inappropriate. In any event, there are no laws, regulations or rules that preclude FDA from revisiting or altering a request in a Not Approvable letter. Accordingly, we find that the Deputy Director's request for new information in June 2010 did not violate or appear to violate any law, regulation, or rule.

c. Documentation in the Administrative File

The whistleblower alleges that the June 18, 2010 call to Carestream is not adequately documented in the administrative file, in violation of 21 CFR § 10.70. The administrative file contains 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 detailing the images that were requested from Carestream. The file does not contain formal minutes of this telephone call, however.

The OIG reviewed the documentation in the file for P080018. They found that the file did not contain formal meeting minutes from several meetings with the sponsor, but that these meetings were all referenced in the file.[34] 21 CFR § 10.70 states that an administrative file should include minutes of meetings pertinent to significant agency decisions. In the OIG's discussion of the documents that "should reasonably be included in an administrative file," they included minutes of all meetings with sponsors, and said that:

> "Specifically, PMA and 510(k) administrative files should include:
>
> - The contents and dates of any phone calls or other meetings between FDA reviewers and the sponsor."

In this case, the file did not contain a formal document entitled "meeting minutes" but did contain an email describing the contents and dates of the phone call between the Deputy Director, lead reviewer, and Carestream. We find therefore that the documentation in the file of this telephone call, although not ideal, provided substantial compliance with 21 CFR § 10.70, and did not violate or appear to violate any law, regulation, or rule. With respect to the other documents that the OIG found to be missing or unsigned, we find that the failure to have signatures on some documents may have violated § 10.70, but were errors were minor and did not compromise the legal or scientific basis for PMA approval.

IV. Recent CDRH Actions Related to Review of Medical Devices

In August 2010, following extensive public input, CDRH released two reports that identified aspects of its pre-market programs that needed improvement. The reports also proposed potential actions to take to address the underlying root causes.[35] Since that time, CDRH has launched over 35 new initiatives designed to clarify and strengthen procedures related to the review of medical devices. A report entitled "Medical Device Pre-Market Programs: An Overview of FDA Actions"[36] provides a detailed description of the actions CDRH has taken and plans to take is

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[34] The OIG further found that certain other minutes were not signed and that an email between the sponsor and FDA was mentioned but not included. The Carestream device file included all letters and emails summarizing the deficiencies in the PMA submission and all other documentation of the reviewers' analysis. However, five Review Team Memorandums included in the file were not signed. In addition, an Information Letter to the lead investigator at one of the clinical investigation sites concerning a data audit was mention in the FDA Review Memorandum but was not in the file. All other standard documents were in included in the file.

[35] CDRH Preliminary Internal Evaluations—Volume I: 510(k) Working Group: Preliminary Report and Recommendations, August 2010.; available online at http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDRH/CDRHReports/UCM220784.pdf; CDRH Preliminary Internal Evaluations—Volume II: Task Force on the Utilization of Science in Regulatory Decision Making: Preliminary Report and Recommendations, August 2010; available online at http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDRH/CDRHReports/UCM220783.pdf.

[36] CDRH, Medical Device Pre-Market Programs: An Overview of FDA Actions, Oct. 19, 2011; available online at http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDRH/CDRHReports/ucm276

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. The actions listed below represent only a small number of those undertaken, but are particularly relevant to the issues discussed in this report.

1. As described in section II.E.4 of this report, in December 2011, FDA issued new draft guidance on evaluating substantial equivalence in 510(k) reviews.[37] The purpose of the draft guidance is to provide greater clarity with respect to FDA's review process for evaluating substantial equivalence. It is not intended to implement significant policy changes to the current review process.

2. In March 2012, FDA published a first-of-its-kind guidance document describing how the benefits and risks of certain medical devices are considered during pre-market review.[38] The guidance:
   - outlines the systematic approach FDA device reviewers take when making benefit-risk determinations during the premarket review process;
   - provides manufacturers a helpful tool that explains the various principal factors considered by the agency during the review of PMA applications, the regulatory pathway for high-risk medical devices, and de novo petitions, a regulatory pathway available for novel, low- to moderate-risk devices; and
   - describes an approach that takes into account patients' tolerance for risks and perspectives on benefits, as well as the novelty of the device.

   This guidance is intended to provide CDRH reviewers with uniform and consistent guidelines to assess probable benefits and risk, and to provide manufacturers with greater predictability, consistency and transparency in FDA decision-making.

3. CDRH has implemented two new Standard Operating Procedures (SOPs) this month:

   - The first SOP is intended for use by CDRH staff for compiling the Administrative File of premarket submission decisions.[39] FDA regulations require adequate

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272.htm. The implementation of many of these actions is tracked at CDRH's webpage: Accomplishments: CDRH Plan of Action for 510(k) and Science: http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDRH/CDRHReports/ucm276286.htm.

[37] FDA, Draft Guidance for Industry and Food and Drug Administration Staff – The 510(k) Program: Evaluating Substantial Equivalence in Premarket Notifications [510(k)], December 27, 2011; available online at: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm282958.htm.

[38] FDA, Guidance for Industry and Food and Drug Administration Staff, Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approval and De Novo Classifications, March 28, 2012.; available online at http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm297411.htm.

[39] This SOP is available on request from Philip.Desjardins@fda.hhs.gov.

documentation of all significant decisions in a complete Administrative File. This 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. This SOP was developed as one of CDRH's internal priorities for Fiscal Year 2012 as part of a continuous quality improvement effort. It also takes into consideration new documentation requirements under the Food and Drug Administration Safety and Improvement Act.

- The second SOP is intended for resolution of internal differences of professional opinion and provides an approach for documentation of associated scientific, clinical and regulatory findings, perspectives and opinions.[40] Given the complex, multi-layered nature of decision-making and the diversity of expertise of CDRH staff, it is expected that differences of professional opinion will arise in the normal course of business. These differences may be scientific, clinical, or regulatory in nature, or some combination of the three. When differences of professional opinion arise between peers or between an individual and their next-level manager or supervisor and 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.

[40] CDRH, Standard Operating Procedure (SOP) for Resolution of Internal Differences of Opinion in Regulatory Decision-Making; Updated 9/4/12; available online at: http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDRH/CDRHOmbudsman/UCM183860#Section1_Purpose.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

OFFICE OF INSPECTOR GENERAL

WASHINGTON, DC 20201

SEP 21 2012

TO: Kathleen Sebelius
Secretary

FROM: Daniel R. Levinson
Inspector General Daniel R. Levinson

SUBJECT: Office of Inspector General Response to the U.S. Office of Special Counsel Referral: Review of Three Medical Device Files Identified in FDA Whistleblower Allegations (OEI-04-10-00481)

I am writing in response to your request dated June 14, 2012, to respond to an Office of Special Counsel (OSC) letter pursuant to 5 U.S.C. § 1213 regarding allegations made by a whistleblower concerning the Food and Drug Administration (FDA). The allegations relate to FDA's regulatory processes used to approve and clear certain medical devices. According to OSC's letter dated May 31, 2012, the whistleblower alleged that:

1. FDA reviewers used the 510(k) review process to assess colonography devices (in this instance, a picture archiving and communications system device) that required a more stringent level of review prior to clearance;
2. the improper clearance of the colonography devices led to their use on asymptomatic patients, potentially exposing millions of otherwise healthy people to unnecessary radiation and creating a significantly increased cancer risk which, the whistleblower estimates, could result in an increase of approximately 7,000 cases of colon cancer per year; and
3. FDA reviewers approved a digital mammography system despite the fact that the manufacturer failed to provide adequate clinical data to support the safety and effectiveness of the system after its original application was found deficient.

According to the OSC letter, the whistleblower also alleged that the administrative files for the colonography and mammography devices do not include appropriate documentation of FDA's decision to approve or clear the devices.

In a memorandum dated July 25, 2012, I provided an interim response to your request and described the Office of Inspector General's (OIG) plan to address the whistleblower's allegations. On August 6, 2012, OSC granted an extension for the review, and you requested that we report our findings to you no later than September 24, 2012.

As described in the July 25, 2012, memorandum, important aspects of the whistleblower's allegations require an assessment of FDA's reliance on certain clinical data and the relative safety of the medical devices. OIG staff do not have the scientific expertise to make this assessment, nor is OIG authorized under the Inspector General Act (5 U.S.C. App.) to assume responsibility for program decisions vested in the agency.

Taking into account these limitations and OSC's request, we reviewed the administrative files for the devices in question to report on documentation in the administrative file relating to the devices' approval or clearance. Consistent with our expertise and jurisdictional limitations, our review did not make any conclusions as to whether the devices were appropriately approved or cleared.

We found that most of the documents we determined should reasonably be included in the administrative files for the devices referenced in the whistleblower's allegations were present; however, at least one document was missing in each of the files. These missing documents do not necessarily indicate that FDA's decisions to approve or clear the devices were not supported by other documentation in the file. The full results of our review are included in Attachment A to this memorandum. Our interim response, dated July 25, 2012, is also attached.

If you have any questions, please contact me, or your staff may contact Gregory E. Demske, Chief Counsel to the Inspector General, at (202) 205-0568 or by email at Gregory.Demske@oig.hhs.gov.

Attachment A: OIG Response to the OSC Referral: Review of Three Device Files Identified in FDA Whistleblower Allegations

Attachment B: OIG Interim Response dated July 25, 2012

Attachment A

Office of Inspector General Response to the U.S. Office of Special Counsel Referral Letter: Review of Three Medical Device Files Identified in Recent FDA Whistleblower Allegations (OEI-04-10-00481)

This review is in response to a request from the Secretary of Health and Human Services (HHS) dated June 14, 2012, to respond to an Office of Special Counsel (OSC) letter pursuant to 5 U.S.C. § 1213 regarding allegations made by a whistleblower concerning the Food and Drug Administration (FDA). The allegations relate to FDA's regulatory processes used to approve and clear medical devices.

Important aspects of the allegations require an assessment of FDA's reliance on certain clinical data and the relative safety of the medical devices. The Office of Inspector General (OIG) does not have the scientific expertise to make this assessment, nor is OIG authorized under the Inspector General Act (5 U.S.C. App. 3) to make or reverse program decisions made by the agency.

With these limitations and in accordance with OSC's request, we reviewed the administrative files for the devices in question to (1) determine whether they included documents that should reasonably be included in the file and (2) identify information in the administrative files relevant to FDA's decision to approve or clear a device for screening asymptomatic patients. Consistent with our jurisdictional limitations, our review does not make any conclusions as to whether the devices were appropriately approved or cleared.

We reviewed the following administrative file for the mammography device, approved through the premarket approval (PMA) process, that was identified in the whistleblower allegations:

- PMA application P080018 for Carestream Health, Inc.'s KODAK DirectView CR Mammography System, received by FDA's Center for Devices and Radiological Health (CDRH) on July 28, 2008 (Carestream device).[1]

We also reviewed the following two administrative files for a picture archiving and communications system device (Viatronix device), cleared through the 510(k) process, that was identified in the whistleblower allegations:

- 510(k) application K020658 for Viatronix V3D Colon, a device for the display and visualization of medical image data derived from computed tomography (CT) and magnetic resonance (MR) scans, received by CDRH on March 1, 2002; and
- 510(k) application K040126 to update the Indications for Use statement for the 2002 Viatronix V3D Colon, received by CDRH on January 20, 2004.[2,3]

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[1] The Carestream device is a Class III device and was approved through the PMA review process.

We reviewed two administrative files for the same picture archiving and communications system device because, after the device was originally cleared, the sponsor submitted a separate 510(k) submission containing new information to change the Indications for Use.

Although we found most of the documents we determined should reasonably be included in the administrative files for the devices referenced in the whistleblower's allegations, at least one document was missing in each of the files. These missing documents do not necessarily indicate that FDA's decisions to approve or clear the devices were not supported by other documentation in the file.

We also found that FDA reviewed evidence to support a new Indications for Use statement before the evidence was included in an official 510(k) submission. After reviewing the evidence, FDA invited the sponsor to send an official 510(k) submission to change the Indications for Use. The sponsor did so and FDA subsequently cleared the change. The Reviewer Memorandum documenting that FDA reviewed the new evidence was not included in the appropriate file.

Additionally, documents in the file confirmed that when FDA cleared the revised Indications for Use statement of the Viatronix device in 2004, FDA considered the labeling change to encompass screening of asymptomatic patients. The Viatronix device displays images derived from a CT scanner, a separate device with a separate classification that is used in conjunction with imaging devices such as the Viatronix device. CT scanners are not cleared for specific disease diagnosis or specific screening indications but instead are cleared for broad imaging uses.[4]

Our review did not make any conclusions as to whether the devices were appropriately approved or cleared.

BACKGROUND

CDRH is responsible for approving and clearing the devices included in this report. A medical device is generally defined as "an instrument, apparatus, implement ... or other similar or related article, including any component, part, or accessory, which is ... intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease... ."[5] Devices vary in complexity and application, ranging from simple tongue depressors to complex pacemakers. A device's risk classification (i.e., Class I, Class II, Class III) generally determines whether it will undergo the PMA or 510(k) review process.[6]

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[2] The 2002 and 2004 administrative files for the Viatronix device were, respectively, 702 and 764 pages in length. The administrative file for the Carestream device contained 8,356 pages.

[3] The Viatronix device is a Class II device and was cleared through the 510(k) process.

[4] A CT scanner is not used for the display and visualization of medical image data and is not listed as a predicate in the 2002 or 2004 Viatronix device 510(k) submissions.

[5] Section 201(h) of the Federal Food, Drug, and Cosmetic Act (FFDCA) (21 U.S.C. § 321(h)).

[6] 21 CFR § 860.3.

The PMA Process

The PMA review is the most stringent process for obtaining FDA approval to market a device and is required by statute for devices that are high-risk or are not eligible for a less stringent review process.[7] For a device to receive approval via the PMA process, device manufacturers (i.e., sponsors) must submit sufficient scientific evidence to demonstrate a reasonable assurance that it is safe and effective for its intended use.[8] Typically, FDA requires sponsors to submit results of nonclinical laboratory studies and clinical investigations involving human subjects that show the device is safe and effective.[9]

After a sponsor submits a PMA application, FDA performs a preliminary review to determine whether the application is sufficiently complete for scientists with subject matter expertise (reviewers) to begin a substantive review.[10] FDA's substantive review includes inspections of manufacturing facilities; audits of clinical study data; and reviews of statistical, software, and patient labeling information.[11]

During its review, FDA may notify sponsors, through Major and/or Minor Deficiency Letters, of deficiencies in the PMA application and information needed to complete the review.[12] Within 100 days of FDA's beginning the review, sponsors may request a meeting with FDA to discuss its status. Prior to this meeting, FDA must inform the applicant in writing of any identified deficiencies and the information required to address them.[13] If FDA notifies a sponsor that it must submit additional information, or if the sponsor chooses to submit additional information on its own initiative, the sponsor submits amendments to the original application for FDA review.[14] If FDA determines that a device is safe and effective for its intended use, it will send the sponsor an FDA Approval Order.[15]

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[7] Section 515(a) of the FFDCA (21 USC § 360e(a)).

[8] Section 515(c) of the FFDCA (21 USC § 360e(c)) and 21 CFR § 814.20.

[9] 21 CFR § 814.20(b)(3)(v).

[10] 21 CFR § 814.42(a).

[11] For example, see FDA, *Premarket Approval: PMA Review Process*, June 8, 2011. Accessed at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketApprovalPMA/ucm047991.htm on August 13, 2012. Although FDA may refer a PMA application to a panel for review, it did not do so for the PMA application indicated in the whistleblower allegations.

[12] Major deficiencies include significant information such as detailed reanalysis of previously submitted data and additional test data to demonstrate the safety and effectiveness of the device. Minor deficiencies may include clarifications of previously submitted information and revisions to the labeling. FDA, *Guidance for Industry and Staff, FDA and Industry Actions on Premarket Approval Applications (PMAs): Effect on FDA Review Clock and Goals*, June 30, 2008, pp. 3–4. Accessed at http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089734.pdf on August 15, 2012.

[13] Section 515(d)(3) of the FFDCA (21 U.S.C. § 360e(d)(3)); FDA, *Premarket Approval: PMA Review Process*, June 8, 2011. Accessed at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketApprovalPMA/ucm047991.htm on August 13, 2012.

[14] 21 CFR § 814.37(a) – (c). Sponsors may also submit voluntary amendments throughout the review process. FDA, *Guidance for Industry and Staff, FDA and Industry Actions on PMAs: Effect on FDA Review Clock and Goals*, June 30, 2008, p. 13. Accessed at http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089734.pdf on August 15, 2012.

[15] Section 515(d)(2) of the FFDCA (21 U.S.C. § 360e(d)(2)); 21 CFR § 814.44(d)(1).

The 510(k) Process

The 510(k) process is a faster and less-stringent process for obtaining FDA clearance to market a device. By statute, Class I and Class II devices are generally eligible for clearance through the 510(k) process.[16] In the 510(k) process, sponsors do not have to submit scientific evidence demonstrating that a device is safe and effective for its intended use. Instead, sponsors must submit information demonstrating a device is substantially equivalent to a device already being legally marketed (the predicate device).[17]

FDA determines that a device is substantially equivalent to a predicate device if it has the same intended use and technological characteristics as the predicate device. FDA may also determine that the device is substantially equivalent to a predicate device if the devices have the same intended use but different technological characteristics and the information submitted to FDA does not raise different questions of safety and effectiveness from the predicate devices.[18]

Labeling changes to an existing 510(k) device may affect the Indications for Use or intended use. A device's Indications for Use statement is "[a] general description of the disease or condition the device will diagnose, treat, prevent, cure, or mitigate, including a description of the patient population for which the device is intended."[19] Changes to the Indications for Use of a device generally require a new 510(k) submission.[20] A change in the Indications for Use statement is not necessarily a change in a device's intended use.[21] If, however, a sponsor proposes a labeling change that results in a new intended use, then the device may no longer be substantially equivalent and may require a PMA review.[22, 23]

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[16] Section 513(f) of the FFDCA (21 U.S.C. § 360c(f)).

[17] "A legally marketed device to which a new device may be compared for a determination regarding substantial equivalence is a device that was legally marketed prior to May 28, 1976, or a device which has been reclassified from Class III to Class II or I (the predicate), or a device which has been found to be substantially equivalent through the 510(k) premarket notification process." 21 CFR § 807.92(a)(3).

[18] FDA, *Medical Devices: Premarket Notification (510k)*. Accessed at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketNotification510k/default.htm on August 28, 2012. A device cannot be found substantially equivalent to the predicate device if the predicate device has been removed from the market at the initiative of FDA or has been determined by a judicial order to be misbranded or adulterated. 21 CFR § 807.100(b).

[19] 21 CFR § 814.20(b)(3)(i).

[20] 21 CFR § 808.81(a)(3); FDA, *Is a New 510(k) Required for a Modification to the Device?* Accessed at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketNotification510k/ucm134575.htm on August 30, 2012.

[21] 21 CFR § 807.92(a)(5) and 510(k) Working Group, Preliminary Report and Recommendations. August 2010. Accessed at http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDRH/CDRHReports/UCM220784.pdf on September 14, 2012.

[22] 21 CFR § 801.4. The device's intended use refers to the objective intent of the sponsor.

[23] FDA, *Deciding When to Submit a 510(k) for a Change to an Existing Device, 510(k) Memorandum #K97-1* (Jan. 1, 1997), Section A.1. Accessed at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm080235.htm on August 29, 2012.

During its review, FDA may send letters or emails requesting information to address deficiencies in the 510(k) submission that the reviewer identified (i.e., the FDA Additional Information Request Letter). Once the reviewer reaches a final decision, FDA managers review the file, including the reviewer's final decision. If FDA determines that a device is substantially equivalent to a predicate device, it sends the sponsor an FDA Clearance Letter.

FDA's Documentation of Medical Device Approval and Clearance

FDA creates an administrative file for each device undergoing the PMA or 510(k) review process. The regulations require FDA to document in the administrative file "every significant FDA decision on any matter under the laws administered by the [FDA] Commissioner."[24] Documentation of a significant decision includes "[a]ppropriate documentation of the basis for the decision, including relevant evaluations, reviews, memoranda, letters, opinions of consultants, minutes of meetings, and other pertinent written documents . . . and [t]he recommendations and decisions of individual employees, including supervisory personnel, responsible for handling the matter."[25] Documents that are prepared by agency employees but are not in the administrative file have "no status or effect" for the purpose of approving or clearing the device.[26] However, missing documents do not necessarily indicate that the devices were improperly approved or cleared. Finally, written documents in the administrative file must be signed and dated by the author.[27]

FDA has not defined what constitutes a significant decision as it relates to the device approval or clearance processes. For the purposes of this review, we considered the decisions to approve or clear the devices significant. FDA does not have procedures for documenting the significant decision to approve or clear the device. Further, FDA has not defined, beyond the requirements of 21 CFR § 10.70, the specific documents that must be in administrative files. FDA has not defined written documents that require signatures and dates.

Allegations in the OSC Referral Letter

In accordance with 5 U.S.C. § 1213, OSC referred allegations to HHS that FDA improperly approved the Carestream device and that FDA managers ignored review team concerns that the sponsor failed to provide adequate analytical data in support of its PMA application. Additionally, the OSC referral letter states that an FDA official did not properly document correspondence with the sponsor in the administrative file.

With respect to the Viatronix picture archiving and communications system device, the OSC letter alleges that FDA did not properly clear the device based on several grounds. The sponsor submitted new evidence to FDA to change the Indications for Use for the Viatronix device, originally cleared in 2002, to include screening of asymptomatic patients. The OSC letter alleges that FDA's review of this evidence was inappropriate because the sponsor did not originally submit the evidence in the form of a new 510(k)

[24] 21 CFR § 10.70(a).
[25] 21 CFR § 10.70(b).
[26] 21 CFR § 10.70(d).
[27] 21 CFR § 10.70(c)(2).

submission for agency review. Therefore, according to the allegations in the letter, no regulatory submission was before the agency at the time FDA made the final decision to clear the changes to the Indications for Use. In addition, the letter alleges that the administrative file does not contain complete documentation.

Further, the OSC letter alleges that the Viatronix device should have undergone a PMA review in 2004 because the Indications for Use were different from those of the predicate devices, which, in some circumstances, could lead to a new intended use. By clearing the 510(k) submission, FDA determined that the new Indications for Use for the Viatronix device did not result in a new intended use. OIG did not determine whether the new Indications for Use statement resulted in a new intended use or whether this submission should have undergone a PMA review.

The letter also alleges that FDA did not properly clear or did not clear the Viatronix device for screening asymptomatic patients because the device's Indications for Use state that it can be used to display images from CT scanners. The letter alleges that, when clearing this device, FDA "did not take into account" that CT scanners have not been approved for screening asymptomatic patients.[28] According to the OSC letter, this could expose a large segment of the population to CT scans, thereby increasing the risk of cancer in otherwise healthy patients. The OSC letter also states that the 2004 Viatronix administrative file did not show that FDA cleared the device "to perform screening of asymptomatic patients for colon cancer."

Scope of Inspection

We reviewed the administrative files for the Carestream and Viatronix devices to determine whether documents that reasonably should be included in the administrative files were present. We also reviewed the 2002 and 2004 administrative files for the Viatronix device to identify information included in the file relevant to FDA's clearance of the device for screening asymptomatic patients.

We did not review PMA or 510(k) administrative files identified in the OSC referral letter for devices that were not approved or cleared by FDA.[29] We also did not determine whether FDA's approval or clearance of the devices was appropriate because OIG does not have the scientific expertise to make this assessment, nor is OIG authorized under the Inspector General Act to assume responsibility for program decisions vested in the agency.

Data Collection and Analysis

Because FDA has not defined the specific documents that must be in administrative files, we based our assessment of what documents should reasonably be included in an

[28] CT scanners are Class II devices which are classified and cleared separately from picture archiving and communications system devices such as the Viatronix device. The OSC letter does not allege that CT scanners were improperly cleared.

[29] In the July 25, 2012, memorandum, OIG stated that we would review the administrative files only for PMA application P080018 and 510(k) application K040126. FDA also provided the administrative file for K020658 to provide context for the K040126 file review. FDA later provided the administrative file for K083548, another picture archiving and communications system device, which is not included in our review because it was not cleared by FDA.

administrative file on our review of relevant regulations, prior OIG reviews of 510(k) administrative files, and input from FDA officials during previous work.[30] We determined that documents in PMA and 510(k) administrative files should reasonably include:[31]

1. Documentation of reviewer analysis.[32] Specifically,
    a. PMA administrative files should include:
        - Major and/or Minor Deficiency Letters,
        - amendments and additional information the sponsor submitted to address any deficiencies, and
        - standard review documents (i.e., Lead Reviewer and Review Team Memorandums).
    b. 510(k) administrative files should include:
        - the FDA Additional Information Request Letter,
        - additional information the sponsor submitted to address any deficiencies, and
        - other reviewer documents (i.e., Reviewer Cover Sheet, Reviewer Memorandum, Reviewer Decision Flowchart, Screening Checklist).
2. Minutes of all meetings and all correspondence with sponsors and/or consultations with FDA staff. Specifically, PMA and 510(k) administrative files should include:
    - the contents and dates of any phone calls or other meetings between FDA reviewers and the sponsor,
    - complete email chains between FDA reviewers and the sponsor, and
    - the contents and dates of any internal FDA discussions or consultations, or emails regarding device clearance.[33]
3. Other standard documents pertinent to the decision to approve or clear the device. Specifically,
    a. PMA administrative files should include:
        - the FDA Approval Order,
        - the Medical Device User Fee Form,[34]
        - the original PMA submission from the sponsor,
        - FDA letters to the sponsor regarding findings of certain reviews (i.e., FDA Informational Letter), and
        - Summary of Safety and Effectiveness Data.
    b. 510(k) administrative files should include:

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[30] OIG reviewed 161 510(k) administrative files for the evaluation *FDA's Clearance of Medical Devices Through the 510(k) Process* (OEI-04-10-00480). This evaluation is expected to be issued in December 2012.

[31] We categorized the documents in this manner based on the organization of administrative files and for the purposes of reporting our results. FDA does not formally categorize the documents in this manner.

[32] The focus of this section is on the documents that support the analytical review by the FDA reviewers. Supervisor comments and recommendations, as referenced in 21 CFR § 10.70, may be included in category 1 or 2, depending on whether they are contained in written Review Memorandums or if they were expressed in meetings or correspondence. The FDA's official Clearance Letter or Approval Order is included in category 3.

[33] Opinions of consultants , as referenced in 21 CFR § 10.70, may be included in category 1 or 2, depending on whether they are contained in written Review Memorandums or if they were expressed in meetings or correspondence.

[34] The Medical Device User Fee is required by the Medical Device User Fee and Modernization Act of 2002, P.L. 107-250, and documents that the sponsor paid the user fee, if required.

- the FDA Clearance Letter,
- the Medical Device User Fee Form,
- the original 510(k) submission from the sponsor,
- the 510(k) Summary, and
- the FDA Acknowledgment Letter.

We did not determine which of these documents constitute "relevant evaluations, reviews, memoranda, letters, opinions of consultants, minutes of meetings, and other pertinent written documents" as stated in 21 CFR § 10.70. Rather, we considered all documentation that FDA indicated should be in the file and/or referenced in the file to be relevant and pertinent. We did not determine whether documents submitted by the sponsor were signed and dated.[35] Additionally, we considered all emails included in the file to be signed and dated.

To determine whether FDA cleared the Viatronix device in 2004 for screening asymptomatic patients, we reviewed relevant documents in the 2002 and 2004 files for the Viatronix device administrative files. OIG did not make any conclusions about whether FDA's decision was appropriate.

Limitations

We could not identify certain documents as missing from administrative files if they were not referenced in the administrative file. For example, if FDA held a meeting with the sponsor and there was no reference to the meeting in the administrative file, we would not be aware that the meeting occurred, and therefore, did not report the meeting minutes as missing.

Standards

This review was conducted in accordance with the *Quality Standards for Inspection and Evaluation* approved by the Council of the Inspectors General on Integrity and Efficiency.

FILE FOR THE CARESTREAM DEVICE (P080018)

The Carestream device file included all letters and emails summarizing the deficiencies in the PMA submission and all other documentation of the reviewers' analysis. However, five Review Team Memorandums included in the file were not signed.

FDA did not document meeting minutes from nine meetings with the sponsor and four consultations with FDA staff, although the meetings were referenced in the file. After one meeting with the sponsor, a reviewer emailed the review team supervisor to request the meeting minutes because he was not aware of the meeting. This email was included in the file; however, no response to this email and no meeting minutes were included in the file. The file includes minutes of two additional meetings with the sponsor and one additional consultation with FDA staff, but these minutes were not signed or dated. Further, one email between FDA and the sponsor was referenced in the file but was not documented in the file.

[35] We read the requirements at 21 CFR § 10.70(c) to apply only to records generated by FDA.

The Carestream device file did not include one other standard document. FDA sent 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. This letter was mentioned in an FDA Review Memorandum in the file, but the letter itself was not in the file. All other standard documents were included in the file.

2002 FILE FOR THE VIATRONIX DEVICE (K020658)

In the 2002 file for the Viatronix device, the Reviewer Decision Flowchart was blank—it was not completed, signed, or dated.[36] All other documentation of the reviewer's analysis was in the administrative file.

The 2002 file for the Viatronix device lacked one piece of correspondence between FDA and the sponsor. FDA determined that the original Indications for Use statement was ambiguous and required the sponsor to change the wording of the statement. A document in the 2002 file for the Viatronix device states that an FDA reviewer emailed the sponsor expressing his subsequent approval of changes to the device's Indications for Use.[37] However, the reviewer's email is not included in the file.

The 2002 file for the Viatronix device included all other standard documents. However, the FDA Acknowledgment Letter was not signed.[38]

2004 FILE FOR THE VIATRONIX DEVICE (K040126)

The 2004 file for the Viatronix device was missing one piece of documentation of the reviewer's analysis; the Reviewer Memorandum documenting the review of new evidence that resulted in the change to the Indications for Use was not in the file. The 2004 file for the Viatronix device updated the Indications for Use for the 2002 Viatronix device based on newly submitted scientific evidence. The 2004 file for the Viatronix device states that an FDA reviewer concluded that this evidence was adequate to clear the new Indications for Use. However, no memorandum documenting the review of this evidence is included in the 2004 file for the Viatronix device. We located this unsigned Reviewer Memorandum in the 2002 file for the Viatronix device.

Based on our review of the unsigned Reviewer Memorandum found in the 2002 file for the Viatronix device, we determined that the sponsor submitted the evidence on November 17, 2003, to change the Indications for Use in the 2002 Viatronix submission. The FDA reviewer completed his review of the new evidence on December 4, 2003. In a letter dated December 9, 2003, FDA informed the sponsor that this evidence would

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[36] The Reviewer Decision Flowchart is a visual representation of the logic used to clear the device through the 510(k) process. It is a form for the reviewer to complete and does not contain any space for a signature or date.

[37] FDA was concerned that the original Indications for Use statement could be misinterpreted to permit use of Viatronix in screening asymptomatic patients. The Indications for Use were revised to limit its use as follows: "... for the display and visualization of 3D and 2D medical image data of the colon...for the purpose of screening a colon to detect polyps, masses, cancers and other lesions."

[38] In our review of 161 510(k) administrative files in the evaluation described in footnote 23, none of the Acknowledgment Letters were signed, although there is a space for the author's signature.

support the change in the Indications for Use. In the December 9 letter, FDA invited the sponsor to submit a new 510(k) to formally change the Indications for Use and assured the sponsor that the submission would receive a rapid review. The sponsor then submitted the evidence in the form of a new 510(k) submission on January 15, 2004. The 510(k) submission for the new Indications for Use was cleared by FDA on April 19, 2004.

Some appropriate documentation of the reviewer's analysis was not signed or dated; the Screening Checklist was not signed by the reviewer's supervisor and the document was not dated.[39] The Reviewer Decision Flowchart was filled in but was not signed or dated.

Finally, the 2004 file for the Viatronix device included all other correspondence between FDA and the sponsor and other standard documents. However, the FDA Acknowledgment Letter was not signed.

We also reviewed the file for the 2004 Viatronix device to identify information relevant to FDA's decision to clear the device for screening asymptomatic patients. The Indications for Use cleared in 2004 for the Viatronix device states the device may be used "for the purpose of patient screening for detection of colon cancers, polyps, masses, and other lesions." In the file, FDA states that the Indications for Use statement encompasses screening asymptomatic patients.

According to the OSC letter, the whistleblower also alleges that the Viatronix device cannot be cleared for screening asymptomatic patients because it can be used to display images from CT scanners. The Viatronix device is a picture archiving and communications system device designed to display image data from CT and/or MR scans. Although these devices are used in conjunction with CT scanners, they are separately cleared through the 510(k) process and must be substantially equivalent to different predicate devices. The Indications for Use statement of a CT scanner is generally broad (e.g., "acquisition and display of axial x-ray images of the whole body to include the head") and is not for specific disease diagnosis or for a specific population. As a result, sponsors of CT scanners have not specifically addressed the use of CT scanners in asymptomatic patients. Instead, they must prove the CT scanner is substantially equivalent to a predicate device.[40]

CONCLUSION

This review responds to a request from OSC to investigate allegations made by an FDA whistleblower. The OSC request was received by the Secretary, who requested that the Inspector General conduct a review and report our findings to her. We located most of the documents we determined should reasonably be included in the administrative files for the devices identified in the whistleblower's allegations; however, at least one

[39] The Screening Checklist includes two signature lines, one for the reviewer and one showing concurrence from the Review Branch.

[40] At the time of our review, FDA stated on its Web site, "No data have been presented to the FDA to demonstrate that [CT scanners] are effective for screening, i.e., testing individuals without symptoms." FDA also advised OIG that no manufacturer had made a submission to clear CT scanners specifically for use in asymptomatic patients.

document was missing in each of the files. With respect to the Viatronix device, we found that FDA received a 510(k) application and cleared the device in 2004 for screening asymptomatic patients. Although Viatronix may be used to display image data from CT scanners, those are separate devices, are separately cleared, and must be substantially equivalent to distinct predicates.

Our review did not assess or conclude whether any of these devices were appropriately approved or cleared.

Attachment B

OIG Interim Response dated July 25, 2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

OFFICE OF INSPECTOR GENERAL

WASHINGTON, DC 20201

TO: Kathleen Sebelius
Secretary

FROM: Daniel R. Levinson *Daniel R. Levinson*
Inspector General

SUBJECT: U.S. Office of Special Counsel Whistleblower Referral

DATE: July 25, 2012

I am writing in response to your June 14, 2012, letter concerning a whistleblower disclosure that the U.S. Office of Special Counsel (OSC) referred to you for investigation pursuant to 5 U.S.C. § 1213. The whistleblower alleges that improper conduct by employees of the Food and Drug Administration (FDA) compromised the integrity of the review of certain medical devices. You have delegated your authority to the Office of Inspector General (OIG), asking that OIG conduct "a full and objective investigation" of the allegations raised in the whistleblower disclosure and report the findings directly to you.

As requested, OIG closely analyzed the allegations in the letter from OSC. In response, OIG has undertaken a file review to ascertain whether FDA appropriately documented significant decisions associated with clearance of the identified devices as required by agency regulation. OIG has also concluded that important aspects of these allegations require a scientific assessment of both the reasonableness of reliance on certain predicate devices and the relative safety of the medical devices at issue. OIG does not have the expertise to make this scientific assessment, nor is it authorized to make judgments on agency program decisions. OIG will provide the full results of the file review as soon as it is completed. To accommodate the file review and any scientific assessment, you may wish to request an extension from OSC to reply as authorized by 5 U.S.C. § 1213(c)(1)(B).

Last month, OIG issued an evaluation report on adherence to FDA internal procedures with respect to dispute resolution that, in part, addresses the concerns of OSC. OSC has separately requested the workpapers underlying the evaluation. OIG is in the process of furnishing OSC with these data. A second evaluation is forthcoming that more specifically addresses adequacy of documentation in 510(k) files. OIG will alert you as soon it has a release date for that study.

The following is a fuller explanation of the work that OIG has already done that addresses some of the concerns expressed by OSC and the additional work that OIG has initiated in response to

OSC's recent referral. OIG has also attached an explanation of the limitations on OIG's authorities that preclude it from substituting its judgment for scientific decisionmaking by FDA program officials.

Background

Section 3(a)(13) of the Whistleblower Protection Act of 1989 (Pub. L. 101–12, April 10, 1989) requires OSC to take action on any disclosure by any employee or former employee of information that indicates a "substantial likelihood" of a violation of any law, rule, or regulation; gross mismanagement; a gross waste of funds; an abuse of authority; or a substantial and specific danger to public health or safety. (5 U.S.C. §§ 1213(a)(2) and (b)). Specifically, OSC must transmit the information to the appropriate agency head, who must then conduct an investigation and submit to OSC a written report setting forth any findings. (5 U.S.C. § 1213(c)). OSC then transmits the report, along with any comments received from the whistleblower and any comments and recommendations by the Special Counsel, to the President and the congressional committees with jurisdiction over the agency involved. (5 U.S.C. § 1213(e)(3)).

Under this authority, OSC referred a whistleblower disclosure in OSC File No. DI-11-3325 to the Department of Health and Human Services (HHS) for investigation. The referral alleges that FDA employees responsible for reviewing and clearing or approving medical devices created a substantial and specific danger to public health and safety by ignoring agency device review protocols and violating agency regulations in the clearance of several types of colonography machines for general population screening and the approval of a digital mammography device for the screening and diagnosis of breast cancer. The whistleblower makes three allegations, specifically:

1. FDA reviewers used the agency's 510(k) review process to assess colonography devices that required a more stringent level of review prior to clearance.

2. The improper clearance of the devices led to their use on asymptomatic patients, potentially exposing millions of otherwise healthy people to unnecessary radiation and creating a significant increased cancer risk, which, the whistleblower estimates, could result in an increase of approximately 7,000 cases of colon cancer per year.

3. FDA reviewers approved a digital mammography system for use despite the fact that the manufacturer failed to provide adequate clinical data to support the safety and effectiveness of the system after its original application was found deficient.

OIG addresses each allegation individually below.

The OSC referral calls, in part, for a substantive determination as to whether the scientific assessments made by FDA were appropriate. As explained more fully in the attachment to this memorandum, OIG does not have the authority or expertise to weigh the scientific merits of the devices at issue here nor can OIG determine whether the devices should have been approved.

An independent review of the scientific conclusions reached by FDA would have to be conducted outside OIG. OIG can and will, however (with certain caveats below) review the relevant files to determine whether decisionmaking was documented in accordance with FDA requirements.

Related OIG Work

In June 2012, OIG's Office of Evaluation and Inspections (OEI) issued a report entitled *Scientific Disagreements Regarding Medical Device Regulatory Decisions* (OEI-01-10-00470) (http://oig.hhs.gov/oei/reports/oei-01-10-00470.pdf) (OEI Report). Using the workpapers from this report, OIG has assembled some general information describing the review processes for two colonography devices and the digital mammography device referenced in the referral, K083423, K083548, and P080018, respectively. This OEI evaluation looked at the handling of 36 scientific disagreements reported by FDA's Center for Devices and Radiological Health (CDRH) managers and reviewers. The report examined: (1) what the nature of the disagreements was; (2) whether CDRH followed relevant regulations and procedures in resolving these disagreements; and (3) how it implemented its new procedures for resolving scientific disagreements. The review did not attempt to assess the scientific analyses conducted by the relevant parties or determine whether the ultimate resolutions by CDRH were the correct ones. Relevant portions of this report are included in the discussion of the specific allegations below.

A second report is nearing completion within OIG that looks more directly at documentation of decisions associated with clearing devices through the 510(k) process. More specifically, with respect to various devices cleared through the 510(k) process during 2010, our evaluation examines whether FDA completely documented the significant decisions in clearing the devices and the extent to which FDA documented use of available safety and effectiveness data. There is an important limitation on the OIG work concerning the 510(k) process that will also apply to the file review OIG has undertaken in response to OSC. OIG cannot identify documents that had been *omitted* from the file, unless such documents were referenced in other documents in the file. Absent such references in other documents, OIG would not have the substantive expertise to recognize potential omissions.

Specific Allegations

Colonography Devices – Allegations Relating to the 510(k) Process

The whistleblower alleges that FDA cleared certain colonography devices for general screening use through the expedited 510(k) clearance process, when, in fact, the intended use for general screening necessitated the use of the more stringent Premarket Approval (PMA) process. In the most general terms, FDA's 510(k) process requires device manufacturers to demonstrate that a device is "substantially equivalent" to a "predicate device," meaning that the new device has the same intended use and technological characteristics as a device already being legally marketed or that the device has different technological characteristics but submitted information demonstrates that the device is as safe and effective as the legally marketed

device and does not raise different questions of safety or effectiveness. The PMA process, which usually requires clinical trials, requires device manufacturers to demonstrate that a device is reasonably safe and effective for its intended use. The whistleblower contends that the clearance of these devices and their use for general screening may increase the possibility that individuals will develop cancer, a public health risk.

The crux of the first allegation appears to be whether the file for one device – Viatronix, K040126 – met appropriate documentation standards and whether FDA appropriately concluded that the Viatronix device could serve as a predicate for CT screening of general populations (e.g., asymptomatic patients). The whistleblower cited the following language in the clearance for K040126 for the assertion that the device was not cleared for use in general population screening:

> 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 asserts that the reference to "patient screening" in this sentence does not refer to the general population screening but instead refers to screening of symptomatic patients only.

With respect to documentation, the whistleblower contends that the file supporting the clearance of the Viatronix device violates the documentation requirements in 21 CFR § 10.70. This regulation requires that FDA employees adequately document in the device's administrative file every "significant" decision in clearing a device. Among other things, the file must contain appropriate documentation of the basis for the decision, including the recommendations and decisions of individual employees, including supervisory personnel. The whistleblower maintains that the Viatronix file did not contain a signed review memorandum or similar documentation showing an analysis of the predicate device that would have served as the basis for the decision. It is within OIG's jurisdiction to undertake an examination of whether the Viatronix file met the requirements of 21 CFR § 10.70; OIG is moving forward on such a review. However, each device file contains hundreds or even thousands of pages of documentation. Thus, a complete review of the file cannot be completed within the 60-day period requested by OSC.

As explained previously, the review is, by necessity, restricted to the documents in the file. OIG would not know, for example, if the file did not contain an item that it should (e.g., a recommendation for a different outcome) unless that item were later referenced in another document. With those caveats in mind, OIG has requested the full Viatronix file and will submit a followup report to you as soon as the review is completed.

OIG's recently published report, *Scientific Disagreements Regarding Medical Device Regulatory Decisions* (URL is on previous page), did review potential disputes in certain of the files named

by OSC in its referral. Information collected during that study with respect to these devices is summarized below (again, OSC has requested the accompanying workpapers directly from OIG).

- K083423

  CDRH received 510(k) application K083423 for a CT Tomography Computer Aided Detection system on November 19, 2008. CDRH sent an additional information letter on December 12, 2008, citing an improper predicate device. The applicant responded on March 18, 2009. The review team continued its review through 2009. In December 2009, the review team agreed that another additional information letter should be sent, but disagreed on what deficiencies should be included. The disagreement appears to have been resolved, but no formal document of the disagreement appears in the documents OEI received. The review had not been completed when OEI collected its data in the spring of 2011, and OEI received an incomplete administrative file. In its review, OEI characterized this as a disagreement documented through emails. The device was cleared on May 17, 2011.

- K083548

  CDRH received 510(k) application K083548 for a CT colonography screening device on December 3, 2008. On December 16, 2008, FDA requested additional information from the applicant to identify an appropriate predicate device. A clinical consult was requested for the application, and the consulting clinician found the device to be not substantially equivalent to its predicate because of new indications for use. The lead reviewer assigned to the application disagreed and believed the device to be substantially equivalent. The lead reviewer's manager instructed her to follow prescribed procedures for resolving a disagreement. On April 15, 2009, the lead reviewer wrote a memorandum that recommended a finding of substantially equivalent and acknowledged differences of opinion within the review team. Subsequently, multiple discussions took place between the lead reviewer, consulting reviewer, and management to attempt to resolve the differences of opinion. On April 28, 2009, a second clinical reviewer was brought in to review the file. Both clinical reviewers submitted final memorandums recommending a finding that the device was not substantially equivalent to the predicate device. One of the clinical reviewers accused the lead reviewer and management of misconduct and illegal activity with respect to the application. Multiple exchanges ensued between the review team and management about these differences of opinion.

On June 3, 2009, the lead reviewer revised her recommendation from substantially equivalent to a request for additional information from the applicant. The other members of the review team still disagreed and felt the device was not substantially equivalent. The difference of opinion between the lead reviewer and the review team continued, and the Office Director became involved. The review team and managers met on November 11, 2009, to discuss this disagreement, but the two dissenting reviewers declined to participate. According to meeting

minutes, the consensus of the meeting was to request additional information from the applicant. Subsequently, a separate reviewer was assigned to review the application. On April 8, 2010, this reviewer wrote a memorandum recommending a request for additional information. On April 12, 2010, an official letter was sent to the applicant to request additional information. The applicant did not respond to the request within the required time period; as a result, FDA considered the 510(k) application withdrawn on October 31, 2010.

OIG's ability to review the second issue – whether FDA appropriately concluded that the Viatronix device could serve as the predicate for devices intended for CT screening of general populations (e.g., asymptomatic patients) – is potentially more problematic. This determination may call for an assessment of the scientific justification behind concluding that "patient screening" includes screening of asymptomatic people in the general population. The whistleblower contends that the term must be read more narrowly – that FDA intended to approve screening only symptomatic patients, a reading that would have made the PMA process the appropriate approval vehicle. Again, OIG cannot be the arbiter of a scientific assessment; however, if there is additional clarification in the file, OIG will identify it during its review.

Colonography Devices – Allegation Relating to Health Risk

The whistleblower also alleges that the clearance of CT colonography may have resulted in an increased cancer risk for asymptomatic patients who are screened. According to the whistleblower, regular and repeated use of CT screening is unlikely to identify a serious disease and provides more harm than benefit to asymptomatic persons, claims that the whistleblower states are supported by current research. This is an example of a scientific dispute that falls outside OIG's jurisdiction. OIG has no authority to make this discretionary determination on behalf of HHS; further, OIG does not possess the expertise necessary to weigh the scientific evidence to determine whether a public health risk exists. This decision is the FDA's to make, and the OIG is jurisdictionally restricted from usurping the program's authority.

Mammography Device

The whistleblower alleges that FDA managers circumvented prescribed review and approval procedures in the PMA approval process for a digital mammography device (Carestream device, P080018), despite the review team's concerns that the manufacturer failed to submit sufficient evidence to prove the device's ability to detect microcalcifications of the breast. The use of this device in routine breast cancer screening may, in the opinion of at least one member of the review team, lead to a significant increase in misdiagnoses and failure to detect certain manifestations of breast cancer, a significant public health risk.

As was the case regarding the colonography allegations, OIG's jurisdiction extends to the procedural issue but not the scientific one. OIG is reviewing the Carestream file to determine whether it meets the documentation requirements of 21 CFR § 10.70. The review will determine whether the appropriate documentation of communications and significant decisions appears in the file. Again, this file review will be time intensive and will be limited to the documents in the

file and those that OIG has become aware of because of their reference in other documents. OIG has initiated this review and will keep the Department apprised of its progress.

OIG does not have the authority or the expertise to weigh in on the question of whether FDA correctly determined that the Carestream device was safe and effective, as required by the regulations. The dispute centers on whether the images from six cancer-free patients submitted by the manufacturer constituted valid scientific evidence to make the determination of reliability, an essential component of a finding of safety and effectiveness. The interpretation of "valid scientific evidence" is FDA's, as is the subsequent determination of safety and effectiveness. As a legal matter, OIG may not assume programmatic responsibilities in violation of the Inspector General Act.

Again, the analysis in the recent OEI Report concerning dispute resolution included the Carestream device. Following is a summary of what OIG learned (again, OSC has requested the accompanying workpapers directly from OIG).

- P080018

  CDRH received Premarket Approval application P080018 for a computed radiography mammography device on July 28, 2008. The review team found shortcomings in the application and issued a major deficiency letter on November 11, 2008. After the applicant submitted new data to support the application, CDRH issued a not approvable letter on April 9, 2009. After receiving more data, CDRH continued its review. In April 2010, the lead reviewer recommended another not approvable letter, but the Division Director questioned his methods. The review team continued to recommend a finding that the application was not approvable. In June 2010, another reviewer on the team suggested that the Division Director initiate the formal dispute process. A review team meeting was held on June 23, 2010, at which the lead reviewer changed his recommendation to approvable. The disagreement appears to have been resolved at that meeting, but no document formally addressed the disagreement and its resolution. CDRH approved the device on November 13, 2010. OEI found no record indicating that any party formally initiated the dispute resolution process.

Again, OIG recognizes that this summary does not constitute a full review of the whistleblower's allegation. After studying the details as related by OSC, OIG sees two main issues: whether certain FDA employees circumvented documentation requirements in the approval of the Carestream device and whether FDA correctly determined that the Carestream device was safe and effective, as required by 21 CFR 860.7. OIG is examining the former but does not have the authority to address the latter.

Conclusion

OIG is currently able to briefly describe the review process for the devices mentioned in the whistleblower allegation. To address the allegations more fully, OIG is undertaking further work within its jurisdictional limitations to examine the documentation issues raised. Specifically, OIG will review the files for K040126 and P080018 to ensure that FDA met documentation requirements. OIG will keep you informed as the review progresses. Jurisdictional limitations prevent OIG from investigating other issues, as explained above. You may wish to obtain an independent review of the remaining issues from qualified medical experts.

If you have any questions, please contact me or your staff may contact Gregory E. Demske, Chief Counsel to the Inspector General, at (202) 205-0568 or by email at Gregory.Demske@oig.hhs.gov.

Attachment

Attachment: Office of Inspector General Jurisdictional Limitations

Under the Inspector General Act (5 U.S.C. App. 3), each Office of Inspector General (OIG) is charged with protecting the integrity of programs funded or administered by its parent agency, by undertaking investigations, audits, and evaluations of fraud, abuse, misconduct, and mismanagement in connection with those programs. There are, however, legal limitations on OIG authority. The Inspector General Act generally prohibits this office from assuming day-to-day "program operating responsibilities." (5 U.S.C. App, 3 § 9). In this way, OIG remains objective and independent when it is called upon to audit, investigate, or otherwise review Department of Health and Human Services (HHS) programs.

The legislative history that accompanied the passage of the Inspector General Act best illustrates the limitations that Congress imposed on the programmatic responsibility of the Inspectors General.

> The Inspector General Act authorizes each such IG to promote economy and efficiency in the administration of, and prevent and detect fraud and abuse in, programs and operations of the designated Federal entities. The IGs are intended to act as independent fact-gatherers, with no vested interest in policy, or in particular programs and operations. For example, the conferees do not intend that the IG at the National Science Foundation question the scientific merits of a specific grant or contract proposal or that the IG at the FEC render judgment on the Commission's exercise of discretion in a particular cause or controversy involving enforcement of or compliance with the campaign finance laws. (House Conference Report No. 100-1020, p. 28.)

And further:

> Broad as it is, the [Inspector General's] mandate is not unlimited. Issues requiring substantive or technical expertise will often fall outside his proper sphere. For instance, if the [Inspector General] at the Environmental Protection Agency received a report that a new type of sewage treatment system in Milwaukee was not functioning according to specifications, resulting in dangerous levels of pollution, the [Inspector General] could quite properly decide that responsibility for handling the issue rested elsewhere and make the proper referral. (Senate Report No. 95-1071, p. 28.)

In short, OIG may not substitute its judgment and overrule discretionary decisions made by agency officials with responsibility for HHS programs. OIG may ensure that agency procedures are duly followed and are not corrupted by self-dealing or misconduct.

Attachment B

DEPARTMENT OF HEALTH AND HUMAN SERVICES

OFFICE OF INSPECTOR GENERAL

WASHINGTON, DC 20201

MAY - 7 2014

The Honorable Carolyn Lerner
Special Counsel
U.S. Office of Special Counsel
1730 M Street, N.W. Suite 300
Washington, D.C. 20036-4505

Dear Ms. Lerner:

In June 2012, you forwarded to the Secretary of Health and Human Services (HHS), Kathleen Sebelius, a whistleblower disclosure alleging improper conduct by employees of the Food and Drug Administration (FDA). In accordance with 5 U.S.C. § 1213, you requested that the Secretary investigate FDA's review of certain applications for premarket approval or clearance of specific medical devices and report back to you. Initially, the Secretary asked that the HHS Office of Inspector General (OIG) investigate. Our attorneys assessed the allegations and concluded that some exceeded the jurisdiction of the OIG. We so advised the Secretary by interim response dated July 25, 2012, and proceeded to conduct a review of those matters that were within our authority. Secretary Sebelius then asked the Commissioner of Food and Drugs to investigate the regulatory matters posed by your letter that exceeded our authority. The inquiries by both FDA and OIG were completed; after a brief extension (granted by your office), on October 1, 2012, the Secretary transmitted to you the reports of both offices.

On March 28, 2014, we learned that your staff had emailed Dr. Peter Lurie, Associate Commissioner for Policy and Planning at FDA, posing 15 follow-up questions to the 2012 reports. Four of these questions addressed the scope of OIG jurisdiction and whether we had properly interpreted and exercised our authorities in this matter, or posed factual questions about our review.

By law, statutory Inspectors General are subject to supervision only by the head of their agency and not by subordinate agency officials.[1] Even the Secretary may not "prevent or prohibit the IG from initiating, carrying out, or completing any audit or investigation." Thus, since the decisions challenged in the follow-up email from your office were made solely by the OIG, these four questions have been forwarded to my office for response.

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[1] The Act states that that each IG "shall report to and be under the general supervision of the head of the establishment involved or, to the extent such authority is delegated, the officer next in rank, but shall not report to, or be subject to supervision by, any other officer of such establishment." (IG Act, § 3(a), 42 U.S.C. App. 3, § 3(a)).

First, as drafted, the question seems to ask whether FDA gave consideration to having the OIG engage expert consultants for the instant review. As mentioned above, the IG reports to and is supervised only by the Secretary. Accordingly, FDA officials could not compel the OIG to engage an expert consultant.

The IG Act does authorize the OIG to "enter into contracts and other arrangements for audits, studies, analyses and other services." (IG Act, § 6(a)(9)). Under this authority, we often engage experts to assist in ongoing investigations, audits or evaluations that are within our jurisdiction. For example, we frequently contract with medical experts who opine on whether health care items or services provided to a Medicare beneficiary were "reasonable and necessary for the diagnosis or treatment of illness or injury," as is required by law. Where the provider's care was found to be medically unnecessary, we recommend to the program agency that it recover payment for those services. In egregious cases, we pursue civil or criminal false claims cases.

In contrast, we know of no instance in which the OIG has, under its contracting authority or otherwise, rendered judgment on the discretionary decision made by an authorized HHS official (e.g., selection of a contractor or grantee; approval of a medical device or new drug). Again, we do not have authority to make or reverse those determinations that are vested in agency management and so would not engage an expert to do so.

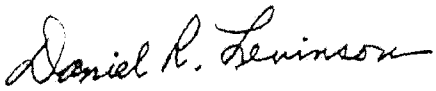
The OIG does not shy away from inquiries or reviews simply because they involve technical scientific issues. As the Inspector General for a department that runs hundreds of health and social services programs, we encounter complex medical issues daily. What we decline to do is to make conclusions concerning the safety or effectiveness of a particular device or substitute our judgment for the decision to approve or not approve that device. To be clear; it is entirely legal and appropriate for authorized FDA officials to weigh the relative merits of an application and exercise discretion to approve or not approve a particular device. The OIG would not investigate an FDA determination simply because there is professional disagreement in the scientific community concerning the device. The OIG could inquire to ensure that the agency followed established procedures in reaching those decisions; but we may not commandeer the FDA's authority to make the decision and we may not reverse the decision once made.

Question 11: ***"Page 7 of the OIG interim report references a June 23, 2010, review team meeting at which the lead reviewer changed his recommendation to issue a second Not Approvable letter to approve the Carestream device. According to the report, the "disagreement [over whether to approve the device] appears to have been resolved at that meeting," however, there was no documentation in the file addressing the disagreement and its resolution. If the June 23 meeting was not documented, how did the OIG review team arrive at the conclusion that the disagreement was resolved at that meeting and how it was resolved?"***

The OIG's interim response to the Secretary dated July 25, 2012, described a review team meeting held on July 23, 2010. (Our interim response mistakenly described that meeting as having occurred on June 23, 2010.) The minutes of that July 23, 2010 meeting were in the file and included a description of how the disagreement was resolved. The FDA Review of

We hope that you find the above information helpful. If you have questions or would like additional information concerning reports of the OIG, please contact our office directly; you may contact me or our Chief Counsel, Gregory Demske. Mr. Demske may be reached at gregory.demske@oig.hhs.gov.

Sincerely



Daniel R. Levinson
Inspector General

Enclosure

Attachment C

CDRH Meeting Minutes
Carestream

Date: 07/23/2010

Time: 1:30 p.m. – 2:20 p.m.

Participants: Helen Barr, Charles Finder, Thomas Gwise, Paul Hardy, Michael O'Hara, Nicholas Petrick, Mary Pastel, Don St. Pierre, and Matthew Walker

Device: **Carestream Full Field Digital Mammography System.**

Summary of Discussion:

The Acting Division Director, Don St. Pierre, started the meeting by asking the lead reviewer (Paul Hardy) what his recommendation will be for the submission. Paul said that he had not finished his review. Don said that was fine, but he must know what his recommendation is going to be. Paul said that the file is not approvable based upon poor results in the comparative feature analysis related to detecting microcalcifications.

Don summarized the previous discussion that was held with the team on June 2. This discussion involved the clinical and statistical issues surrounding the microcalcification issue, and an approach was discussed on how to resolve these outstanding issues. That approach included obtaining images for the clinician to review.

Don said that it is his understanding, according to a recent email from Thomas Gwise (statistician), the device "has met the Sensitivity and Specificity endpoint for BIRADS 3 which supports the claim that the device is safe and effective". This assertion pertaining to the statistical review was confirmed by Dr. Gwise during the meeting. Furthermore, clinical images supplied by Carestream at the request of the review team were reviewed by Helen Barr (Radiologist and Mammographer) and found to be of diagnostic quality. Helen Barr, the clinical expert, also recommended approval of the device. Don expressed some concern about Paul's not approvable recommendation since his issue was a clinical and statistical issue, and the clinical expert and the statistician were both recommending approval.

Paul again said that he based his recommendation on the results the Carestream system had and the fact they had not addressed the outstanding deficiency from the Not Approvable Letter with regards to imaging microcalcifications and the recommendation of his clinical reviewer, Dr. Smith. Don reminded Paul that Dr. Smith is not a mammographer and Helen Barr and Charles Finder are both mammographers. He also articulated that Dr. Smith's opinion is months old and did not incorporate the latest data submitted by the sponsor. A discussion of the history of cleared FFDM devices and their ability to detect microcalcifications ended with Helen Barr, Charles Finder and Mary Pastel stating that it is well known that microcalcification detection with FFDM devices is somewhat less than with film-based mammography systems. Helen said that the cases submitted did contain microcalcifications, albeit ones unlikely to be malignant, but that the assessment of microcalcifications was the same no matter what they turned out to be, and

that the images she reviewed, revealed that the Carestream device is similar to devices already on the market and that she believes that the images are of diagnostic quality. She also expressed concern that in the non-approvable letter to Carestream the trend described above was characterized as "strong", when in fact it was "minimal to mild", and that she did not believe that such a trend was clinically important.

Don asked Paul to clarify his "not approvable" recommendation in light of this discussion and the recommendations from Thomas Gwise and Helen Barr. Don said that he was having a hard time understanding why Paul appears to have a different opinion from the clinical consultant and he wanted to fully understand his recommendation. Paul said that Don St. Pierre did not agree with his opinion at the last meeting. Don and Paul agreed at that meeting that the review of the images by Helen Barr would be an important component of the final decision for the Carestream device. There was a discussion of false positives and false negatives. This discussion ended when Helen said that she did not feel that this device will miss more cancers than devices already on the market. Dr. Finder stated that in reviewing the data from Fuji compared to this device in regards to a trend towards screen-film, this device appears to actually perform better. Dr. Barr mentioned that an analysis done by her program of recent phantom image scores revealed that phantom image scores are increasing due to digital units, despite that units with stronger trends toward the preference for film-screen over digital were on the market and included in this analysis, indicating again in her opinion that this preference is not clinically important.

Don said that the statistics consultant says safe and effective, the clinical consultants say safe and effective and there are no engineering issues with the device and he didn't understand Paul's conclusion. He repeated that the experts were saying something different from Paul's recommendation. In response, Paul said that there are new issues that the discussion brought to light and that he had to reevaluate his opinion. Paul said that he now feels comfortable with the microcalcification issue. Helen said that images of diagnostic quality are, by definition, ones that would be acceptable to assess microcalcifications or any other lesion.

Paul said he would recommend approvable and that he would have a draft review memo by Friday afternoon.
The meeting was adjourned at 2:18PM.

Action Item #1:	Action:
Draft Memo	Paul Hardy will submit a draft review memo on Friday, July 23 to Don St. Pierre.

Note:
A+'s primary purpose for attending the meeting was to provide management with a summary of the proceedings and to ensure the tenor of the meeting remained professional at all times and ensure the meeting attendees all treated each other with respect and professional courtesy. A+'s observation was that the meeting was productive and was carried out in a very professional and collegial fashion.

Attachment D

Meetings Identified by OIG as Lacking Formal Minutes

1. External meeting between FDA and sponsor, July 31, 2007. According to a sponsor submission, "July 31, 2007 meeting notes sent from S. Pate, Carestream Health to H. Lerner, R. Smith, T. Gwise and K. Chakrabarti, DRARD on August 28, 2007." No meeting notes from the sponsor or FDA were found in the PMA file, but Lerner, Smith, Gwise, and Chakrabarti were presumably the FDA participants in the meeting. According to the sponsor submission, FDA agreed at the meeting that the breast composition of the screening population in the original clinical study was acceptable.

2. External meeting between FDA and sponsor, March 28, 2008. A sponsor submission states: "Based on a suggestion by FDA (FDA meeting minutes 03/28/08), Carestream identified a subgroup to exclude from the analysis that had a dose ratio higher than 1.15 per subject [CR dose)/(SF dose)]." No meeting minutes were found in the PMA file. No further information about this meeting is available.

3. Internal meeting or phone call, date unknown. According to Paul Hardy's memo dated November 1, 2008, recommending a Major Deficiency Letter, he "consulted" Dave Buckles, "Acting Radiological Devices Branch" [sic], to ask about waiting until the Establishment Inspection Report to make a final determination about a potential data integrity issue.

4. Internal teleconference between FDA inspectors, October 23, 2008. According to an email dated October 23, 2008, from Barbara Breithhaupt to Paige Wilson and Marilyn White, cc's to Kim Rice, Kathy Martin-Weis, Christine Smith, Kirk Sooter, Linda Godfrey, and Contress Braxton, this was an internal closeout discussion of data integrity issues and potential misconduct by individual at a clinical study site.

5. External meeting between FDA and sponsor, December 15, 2008. This meeting is mentioned in an email, dated December 22, 2008, from Charlotte Baker, Carestream, to Toby Lowe, FDA, with cc's to Paul Hardy and Robert Smith, in which the Ms. Baker relays a short note to Dr. Smith from a Carestream researcher. The note thanks Dr. Smith for meeting with the sponsor the previous Monday "to discuss a proposal for an alternate look at Carestream's Comparative Features Study," and seeks another meeting with him. The email says that the sponsor will get meeting minutes to FDA by December 19. No meeting minutes from the sponsor or FDA were found in the PMA file.

6. External teleconference between FDA inspectors and Dr. Hamm, Clinical Site director, date unknown, in follow-up to a letter from FDA, dated February 25, 2009. This call is mentioned in an internal memo to the Director, DRARD, which includes a description of FDA's audit of PMA data. According to the memo, in the phone call, Dr. Hamm described changes he planned to make to prevent recurrence of FDA observations during PMA data audit.

7. Internal phone call, March 10, 2009. This call, between the Lead Reviewer and Ms. Braxton, is mentioned in a memo from the Lead Reviewer, dated March 8, 2009, but signed March 20, 2009 (perhaps explaining the discrepancy between the date of the phone call and the date of the memo). According to the memo, the two participants discussed an informed consent issue.

8. External phone call between Joshua Nipper and Joyce Whang, FDA and John Pardo and Jeffrey Byng, Carestream, May 19, 2009. A letter from the sponsor requesting informal supervisory reconsideration of the Not Approvable letter states that the request is a "follow-up" to this teleconference. No further information about this teleconference is available.

9. Internal meeting on June 2, 2010. Meeting is mentioned in: (1) the Lead Reviewer's memo, dated August 16, 2010, recommending approval; (2) a memo to the record by Robert Smith dated June 9, 2010; and (3) an email from Paul Hardy to Mr. St. Pierre and Dr. Helen Barr, with cc's to Dr. Mary Pastel, Dr. Michael O'Hara, Dr. Gwise, Dr. Smith, Dr. Feuerstein and Dr. Chakrabarti. According to Dr. Smith's memo, the meeting was attended by Mr. St. Pierre, Dr. Mary Pastel, Dr. Michael O'Hara, Dr. Helen Barr, Mr. Hardy, Dr. Gwise, Dr. Smith, Dr. Feuerstein and Dr. Chakrabarti, and Mr. St. Pierre disagreed with Mr. Hardy's recommendation in his review memo [to send a second Not Approvable letter and seek additional MCC cases]. According to Paul Hardy's email, "it was discussed obtaining images, but it was not determined specifically which ones (e.g., malignant MCC)." An email from Dr. Barr dated June 16, 2010 appears to corroborate that the plan coming out of the meeting was obtaining additional images from the sponsor.

10. Internal meeting, date unknown, discussed in minutes of the July 23, 2010 internal meeting:

    > Paul said that Don St. Pierre did not agree with his opinion at the last meeting. Don and Paul agreed at that meeting that the review of the images by Helen Barr would be an important component of the final decision for the Carestream device.

    Based on the content, this is, in all likelihood, another reference to the June 2, 2010 meeting described in # 7, above.

11. External meetings between FDA and sponsor, August 4, 2010 and August 9, 2010. Meetings are mentioned in an email to Paul Hardy from John Pardo, Carestream, dated August 11, 2010. According to the email, the meetings included the Lead Reviewer, Dr. Chakrabarti, and Dr. Richard Kaczmarek, and involved discussions about revisions of the QC Manual.

12. External teleconference between FDA and sponsor, October 20, 2010. An email from Richard Kaczmarek, FDA to John Pardo, Carestream, dated October 21, 2010, entitled "Follow Up on T-Conf," refers to a call the previous day, which appears to have been a discussion with the sponsor about suggestions made by Dr. Finder, one of FDA's mammography experts, about the QC Manual.

Attachment E

CARESTREAM
MEETING MEMO

Date of meeting: **August 25, 2009**
Time of meeting: 3:00 PM to 4:00 PM; WO66 RmG508
Subject: P080018/A003 Request for Reconsideration of NOAP Decision
Meeting type: FACE TO FACE

FDA attendees: Center for Devices and Radiological Health (CDRH)
Janine Morris, Acting Division Director, Division of Reproductive, Abdominal, and Radiological Devices (DRARD)
Toby Lowe, Project Manager, DRARD
Michael O'Hara, Acting Branch Chief, Radiological Devices Branch (RADB)
Robert Smith, Medical Officer, RADB
Paul Hardy, Reviewer, RADB
Tom Gwise, Statistician, OSB
Jeff Shuren, Acting Center Director, CDRH

Sponsor Attendees
John Pardo, Director of Regulatory Affairs
Dr. Jeffrey Byng, Business and Systems Development, Mammography Solutions

Background

Carestream Health submitted an amendment to their PMA on 6/11/2009 requesting reconsideration of the 4/9/09 Not Approvable decision P080018. This amendment outlined their contention that the concerns raised by the Agency regarding the comparative feature analysis submitted in the PMA do not justify a Not Approvable decision since the clinical study demonstrated non-inferiority to screen-film through a MRMC study.

Meeting Discussion

Sponsor Comments:
Carestream began by giving a brief background of their PMA efforts including their original PMA (P060032) which was given a Not Approvable decision due to issues with the population used for their MRMC study, and the current PMA (P080018).

They went on to explain their thoughts that the comparative feature analysis measures preference and may not be correlated to performance. They commented that the draft special controls guidance suggests that the MRMC has priority because it suggests that any questions raised by preference data could be answered by performing an MRMC study.

FDA Comments:
The Agency explained that the draft special controls guidance is not finalized yet, and interpretations like these are helpful to give the Agency insight as to how to best revise the document prior to issuing the final version. The current draft asks for bench data and a feature analysis, but retains the option to ask for additional clinical data if needed.

The 2001 guidance document on FFDM submissions is the official current guidance, and does require three components – bench testing, MRMC study, and Comparative Feature Analysis (CFA). The CFA is intended to show whether the radiologist is able to read one option better than the other, while the MRMC study shows whether the device meets a threshold of sensitivity and specificity. All three components are required and, in this case, it is as if it the CFA was not done at all since the Agency was not able to reach any meaningful conclusions from the data provided.

Sponsor Comments:
The Sponsor asked what the Agency would do if a CFA showed a preference towards screen-film.

FDA Comments:
The Agency stated that, even if bench testing and MRMC were exception, a CFA would still be required under the current guidance. If the CFA interpretation showed a preference towards screen-film, a risk-benefit analysis would need to be done to look at how this affects performance. A sponsor may be able to show that a negative CFA interpretation did not have negative clinical meaning.

Sponsor Comments:
The Sponsor asked for confirmation that the PMA had no outstanding issues associated with the MRMC.

FDA Comments:
The Agency confirmed this, and also noted that the Agency considers the MRMC study performed by the Sponsor to be a model for these types of studies.

Sponsor Comments:
The Sponsor explained that they have done the CFA, but with a different methodology than the Agency would have liked. They questioned whether it was least burdensome to continue trying to answer the questions raised by this alternate methodology.

FDA Comments:
The Agency explained that different methodologies can often be explored and justified by sponsors but, in this case, the Agency does not believe the methodology used provided any meaningful interpretation.

The Agency explained that a Not Approvable decision still provides the Sponsor an opportunity to address the deficiencies, and asked the Sponsor what they believe is the burden of performing the CFA with the Agency's preferred analysis.

Sponsor Comments:
The Sponsor stated that part of the burden is the extra time to market to perform the study, submit to the Agency, and Agency review.

FDA Comments:
The Agency suggested that the data already used in the CFA could be reanalyzed by radiologists with the new methodology. New data would not need to be collected.

The Agency noted that the issues with the CFA pertain only to the lesion conspicuity analysis. The sub-analysis provided in response to the Major Deficiency letter was not sufficient due to both the small sample size remaining after adjustment and the methodology used to amend the data.

The Agency wants to give the Sponsor an opportunity to provide a complete dataset so that a full evaluation is possible and also to have appropriate data for labeling. The CFA is an integral part of determining performance. The Agency does not believe it is overly burdensome to repeat the CFA on the current data using appropriate methodology in order to have an opportunity to look at the results with a full data set.

Conclusions:
The Sponsor maintained their position that performing a new CFA is burdensome and the data provided supports an approvable decision.

The Agency stated that they would consider the request and respond to the Sponsor within two weeks. The Agency stated that the possible outcomes would be maintaining the current Not Approvable decision or reconsideration resulting in either an Approvable letter (with the remaining deficiencies becoming a labeling issue), a Major Deficiency letter, or an Approval Order. The Sponsor maintains their option to file an appeal if they disagree with the outcome.

Meeting was adjourned at 4:10 pm on August, 25, 2009 by the Agency.

Toby Lowe, Project Manager

Drafted: TAL 09/22/09
Reviewed:
Revised:
Revised:
Finalized:

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Attachment F

Hardy, Paul T

From: St. Pierre, Don J.
Sent: Friday, April 09, 2010 3:09 PM
To: Hardy, Paul T
Cc: Pastel, Mary; Becker, Robert; Barr, Helen J; Finder, Charles A.
Subject: FW: Carestream memo

Attachments: Carestream Memo.doc

Hi PJ,

I am not sure that I am comfortable with your approach below. Could you please put in a consult request in CTS to OCER and give the file to Helen Barr. I would like the experts in Mammography to independently review the file and then we can determine next steps. Please also give Helen, Charlie and Mary access to the eRoom so they have access to everything.

I've talk to Mary and Bob about this so they will be able to provide guidance since I will be gone for the next month.

Thanks,

Donald J. St.Pierre
Deputy Director for New Device Evaluation
Office of In Vitro Diagnostic Device Evaluation and.Safety
Center for Devices and Radiological Health
10903 New Hampshire Avenue
White Oak 66, Rm 5682
Silver Spring, MD 20993
301-796-5454 (ph)
301-847-8514 (fax)

From: Hardy, Paul T
Sent: Wednesday, April 07, 2010 4:29 PM
To: St. Pierre, Don J.
Subject: Carestream memo

Hi Don,
I wanted to provide you the short memo I wrote in regards to the Carestream file after our conversation last week about where we are with the file. I hope this will be beneficial for you Let me know if you have any questions.

Thanks,
P.J.

Carestream Memo.doc (235 KB)

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Attachment G

both in the US and abroad, without evidence that cancers are being missed because approved units show this same or an even worse trend, as well as the results of the DMIST study, seem to give us real-world evidence that, even with this trend, this technology is safe and effective. Additionally, a comparative features analysis is only asking the question of whether one has a preference of one or the other of the two being compared. Just because a lesion is seen slightly worse then on the comparison doesn't mean that the characteristics of the lesion can't be adequately assessed for indicators of malignancy. To me it is analogous to doing an ultrasound exam on a patient with two different machines. I may like/prefer the way the images from one machine look over the other, and I may even be able to see things a little better on the images from one machine then another, but that doesn't mean that I can't make a diagnosis on the images from the machine that is not my preference.

- Why is it that a minimal to mildly better preference for screen-film over Carestream for one set of lesions means that the company has not documented reasonable assurance of safety and effectiveness? Is this an accepted standard that reviewers use? Is it evidence based? As an experienced mammographer, I would accept a preference in this range, given the wide range of reader variability, and I would not think that such a preference meant that there isn't a reasonable assurance of safety and effectiveness

- A panel homework assignment to an expert mammographer could be given to look at some of the images containing microcalifications where screen-film was preferred over Carestream. The question could be asked: "Even thought there is a minimal to mild preference for the visualization of the microcalcifications on the screen film exam, can the microcalcifications on the corresponding Carestream images be adequately assessed for characteristics of malignancy?" I would also be glad to look at a sample of such images.

A meeting was convened of the review team on June 2, 2010. At the meeting, the possibility of obtaining images from Carestream was discussed, but it was not specified as to what type (e.g. malignant MCC).

On June 18, 2010, Mr. St. Pierre, John Pardo of Carestream and me were involved in a telephone call. Mr. St. Pierre requested that the sponsor provide images from six patients with BI-RADS Assessment Categories of 1 or 2 (normal and benign cases respectively). He also asked that: "The image sets should consist of four images: craniocaudal (CC) and mediolateral oblique (MLO) views of each breast. At least three of these image sets should also contain diagnostic images. At least two sets of images should be from patients having fatty breasts and two from patients having dense breasts. Some of the images should also include microcalcifications." Dr. Barr thought that these images should be sufficient.

I stated in a June 21, 2010 e-mail, I did not believe the sponsor could address the outstanding deficiencies related to the detection and characterization of the malignant microcalcifications with only images from six patients and those images being benign and normal cases. I again recommended that the sponsor be sent a Not Approvable Letter with regards to the issue of the trend seen towards screen film for malignant MCC's as the sponsor had not adequately address

Attachment H

CDRH Meeting Minutes
Carestream

Date: 07/23/2010

Time: 1:30 p.m. – 2:20 p.m.

Participants: Helen Barr, Charles Finder, Thomas Gwise, Paul Hardy, Michael O'Hara, **Nicholas Petrick**, Mary Pastel, Don St. Pierre, and Matthew Walker

Device: **Carestream Full Field Digital Mammography System.**

Summary of Discussion:

The Acting Division Director, Don St. Pierre, started the meeting by asking the lead reviewer (Paul Hardy) what his recommendation will be for the submission. Paul said that he had not finished his review. Don said that was fine, but he must know what his recommendation is going to be. Paul said that the file is not approvable based upon the trend seen towards screen film in detecting microcalcifications and the sponsor not adequately addressing outstanding item in the Not Approvable Letter. The sponsor could re-do the study for the microcalcifications by obtaining more cases.

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Don summarized the previous discussion that was held with the team on June 2. This discussion involved the clinical and statistical issues surrounding the microcalcification issue, and an approach was discussed on how to resolve these outstanding issues. An approach that was discussed included obtaining images for the clinician to review.

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Don said that it is his understanding, according to a recent email from Thomas Gwise (statistician), the device "has met the Sensitivity and Specificity endpoint for BIRADS 3 which supports the claim that the device is safe and effective". Furthermore, clinical images supplied by Carestream at the request of the review team were reviewed by Helen Barr (Radiologist and Mammographer) and found to be of "diagnostic quality". Helen Barr, the clinical expert, also recommended approval of the device. Don expressed some concern about Paul's not approvable recommendation since his issue was a clinical and statistical issue, and the clinical expert and the statistician were both recommending approval.

Paul again said that he based his recommendation on the results the Carestream system had and the fact they had not addressed the outstanding deficiency from the Not Approvable Letter with regards to microcalcifications particularly malignant and he had expressed concern and this was recommendation of his clinical reviewer, Dr. Smith. In addition, Paul stated that he did not believe that normal and benign cases could adequately address the outstanding deficiency in the letter. Don reminded Paul that Dr. Smith is not a mammographer and Helen Barr and Charles Finder are both mammographers. A discussion of the history of cleared FFDM devices and their ability to detect microcalcifications ended with Helen Barr, Charles Finder and Mary Pastel stating that it is well known that microcalcification detection with FFDM devices is somewhat less than with film-based mammography systems. Helen said that in terms of microcalcification

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detection, the Carestream device is similar to devices already on the market and that she believes that the images are of "diagnostic quality".

Don asked Paul to clarify his "not approvable" recommendation in light of this discussion and the recommendations from Thomas Gwise and Helen Barr. Don said that he was having a hard time understanding Paul appears to have a different opinion from the clinical consultant and he wanted to fully understand his recommendation. Paul said that he had recommended Not Approvable in his April 7th memo. Don and Paul agreed that the review of the images by Helen Barr would be an important component of the final decision for the Carestream device. Don felt that Paul wanted the review of the images to further clarify his decision. A discussion of the false positives and false negatives ended when Helen said that she did not feel that this device will miss more cancers than devices already on the market and whether or not they are benign or malignant cases shouldn't matter, as long as they are seen well enough to be characterized. Dr. Finder stated that in reviewing the data from Fuji compared to this device in regards to a trend towards screen-film, this device was actually better.

Don said that the statistics consultant says safe and effective, the clinical consultants say safe and effective and there are no engineering issues with the device and he didn't understand Paul's conclusion. He repeated that the experts were saying something different from Paul's recommendation. In response, Paul said that there are new issues that the discussion brought light and that he take the recommendations that the device demonstrated a reasonable assurance of safety and effectiveness into consideration. Paul said that he thinks the issue in regards to the microcalcifications has been addressed by the consultants now on the file. Helen said that images of diagnostic quality are acceptable to assess microcalcifications.

Paul said he would recommend approvable based on the consultants' recommendations and that he would have a draft review memo by Friday afternoon and a final review memo by Monday.

The meeting was adjourned at 2:18PM.

Draft Memo	Paul Hardy will submit a draft review memo on Friday, July 23 to Don St. Pierre.

Final Memo	Paul Hardy will submit a final review memo on Monday, July 26 to Don St. Pierre and the review team.

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Comment [P1]: See edits above, I did not think that the review of normal cases could address the issue.

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Comment [P2]: I don't recall saying this, I remember that Don had asked for a draft and I asked until Monday and he requested for me to send him a draft by the end of Friday which I did.

Comment [P3]: See above comment