FDA U.S. FOOD & DRUG ADMINISTRATION

September 19, 2017

The Honorable Edward J. Markey
United States Senate
Washington, D.C. 20510

Dear Senator Markey:

Thank you for your letter dated June 29, cosigned by several of your colleagues, regarding concerns about lead testing systems manufactured by Magellan Diagnostics, Inc. (Magellan). This response is on behalf of the Food and Drug Administration (FDA or the Agency). The Centers for Disease Control and Prevention (CDC) responded separately.

On May 17, 2017, FDA issued a safety communication to warn laboratories and health care professionals not to use Magellan's LeadCare Systems tests with blood samples drawn from a vein (venous blood).[1] This safety issue came to light as part of FDA's review of an application by Magellan in March 2017; the Agency's investigation of the issue remains ongoing. Please see the enclosed appendix for more information about Magellan's LeadCare Systems and the timeline of FDA's investigation.

The catalyst for FDA's inquiry was Magellan's submission of a premarket notification (510(k)) that sought clearance for proposed changes to two of the company's blood lead testing systems—the LeadCare Ultra and LeadCare Plus. FDA's review team identified concerns with the premarket submission. FDA then sought additional information about the performance of these tests, the company's other LeadCare testing systems, and the company's methodology for risk assessment. FDA determined that Magellan's LeadCare testing systems, when used with venous blood, may significantly underestimate blood lead levels, in some cases posing a serious public health risk. Based on currently available information, FDA believes Magellan repeatedly underestimated the risk to health, as reflected in prior communications to customers and FDA. The safety alert does not apply to capillary blood lead test results collected by fingerstick or heelstick, as FDA currently has no evidence that Magellan's LeadCare testing systems have the same problem when processing capillary blood samples. Concurrent with FDA's safety communication in May, CDC announced retesting recommendations for state and local health departments, health care providers, and laboratories that may have used Magellan's test systems.

FDA continues to actively investigate this issue, including the frequency and extent of inaccurate test results and the effectiveness of mitigating steps that Magellan had previously taken when the company learned of the issue. For instance, Magellan had previously identified use of certain

[1] https://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/ucm558733.htm

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blood collection tubes, including the Becton Dickinson K_2-EDTA Vacutainer tubes, as contributing to inaccurate test results. FDA currently does not have sufficient data to confirm or rule out the use of certain tubes as a root cause, but the Agency is actively evaluating this possibility as part of its investigation into the cause of the inaccurate results. FDA and CDC are working together on studies to help identify the root cause and better characterize the extent of the problem.

As part of the investigation, FDA conducted for-cause inspections of Magellan's facility in North Billerica, Massachusetts, and Becton Dickinson's facility in Franklin Lakes, New Jersey. In both cases, FDA issued a Form 483, the report at the conclusion of the inspection that lists inspectional observations that may be violations of law. On July 13, the Agency released a copy of Magellan's Form 483, which includes nine observations.[2] On August 16, FDA released a copy of Becton Dickinson's Form 483, which cited seven observations.[3] It remains unknown whether certain blood collection tubes, such as Becton Dickinson's K2-EDTA Vacutainer tubes, contributed to the inaccurate test results. The Agency is also carefully reviewing the evidence collected during the inspections to determine if there have been violations of federal law and appropriate next steps.

FDA is also evaluating whether other diagnostic devices should be evaluated in light of the information that the Agency learns from its investigation into the cause of the inaccurate Magellan lead test results. If FDA identifies other devices that could raise similar issues, the Agency will work with the manufacturers, as appropriate, to address any potential problems.

With respect to the next actions the Agency may consider, when it is consistent with the public health protection responsibilities of the Agency and depending on the nature of the violation, it is FDA's practice to give individuals and firms an opportunity to take voluntary and prompt corrective action before it initiates an enforcement action. When appropriate, FDA may issue a warning letter to notify a firm of violations and achieve voluntary compliance. FDA's position is that warning letters are issued only for significant violations, which are violations that may lead to enforcement action if not promptly and adequately corrected.

Should FDA conclude that a manufacturer violated the Federal Food, Drug, and Cosmetic Act (FD&C Act), there are a range of enforcement actions that may be considered, including the following: assessing a civil money penalty (see e.g., 21 U.S.C. § 333(f)(1)); seeking an injunction that requires a manufacturer to stop distributing a product in violation of the FD&C Act (see 21 U.S.C. § 332); instituting a seizure of violative product (see 21 U.S.C. § 334); or, when appropriate, recommending criminal prosecution.

Since FDA's investigation remains ongoing, it would be premature to opine on whether the Agency needs any additional authorities or resources to help identify, intervene in, or rectify this type of situation. At the conclusion of the investigation, should the Agency identity additional authorities or resources that would help address such a situation in the future, we will follow up with your offices.

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[2] https://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/ORA/ORAElectronicReadingRoom/UCM566296.pdf

[3] https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-afda-orgs/documents/document/ucm571749.pdf

It is important to note that all medical devices have benefits and risks. FDA weighs probable benefit to health from the use of the device against any probable risk of injury or illness from such use in determining the safety and effectiveness of a device. Once FDA has made its determination, health care providers, patients, and consumers must weigh these benefits and risks when making patient management decisions. However, not all information regarding benefits and risks for a given device may be known before the device reaches the market. New information about a device's safety and/or effectiveness, including subsequent changes made to the device, its manufacturing process, or supply chain, may lead to identification of new safety problems. It is critical for manufacturers to monitor potential problems with their devices, perform a risk assessment when a potential problem is identified, determine the extent of risk and any appropriate actions, and submit accurate reports of a recall or medical device report to FDA.

Thank you, again, for contacting the Agency regarding this important issue. If you have additional questions, please do not hesitate to contact Adriane Casalotti in our Office of Legislation at (301)796-8900. The same letter has been sent to your cosigners.

Sincerely,

Scott Gottlieb, M.D.
Commissioner of Food and Drugs

APPENDIX

Background on Magellan's LeadCare Testing Systems

Magellan makes four testing systems that have been cleared by FDA:

- LeadCare, cleared in September 1997
- LeadCare II, cleared in October 2005
- LeadCare Ultra, cleared in August 2013
- LeadCare Plus, cleared in July 2015

The LeadCare II test can be used at the point of care (e.g., the physician's office or clinic) by staff who do not have special training. This feature helps fill a critical need to ensure that hard-to-reach populations like children, particularly those in low-income households who may not receive routine health care, are tested for lead exposure.

The LeadCare, LeadCare Ultra, and LeadCare Plus tests are used in more complex laboratories, such as hospital, state, and public health laboratories.

All of the LeadCare devices are FDA-cleared for testing both capillary and venous blood.[4] None of the LeadCare Testing Systems have been used as a predicate in a 510(k) submitted by other manufacturers for a device that FDA subsequently cleared.

In addition, lead tests that use different types of technologies remain available to those who need them. But these tests are typically performed at larger laboratories because of the level of skill needed to perform them.[5]

Timeline

Below is a timeline of events that FDA uncovered as the investigation unfolded, and which supported the May 2017 safety communication. FDA's investigation remains ongoing.

- In November 2014, Magellan sent a Notice to Customers that stated the company "recently identified cases" in which the LeadCare Ultra "underestimates the lead concentration of some blood samples when the sample is analyzed immediately after being mixed with the LeadCare Ultra treatment reagent." The notice instructed customers to implement a 24-hour incubation step with the blood sample to mitigate what the company described as an "infrequent occurrence" that "could impact a small

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[4] Your letter inquired about what guidelines, if any, FDA provides with respect to use of a lead test with different sample types (i.e., venous or capillary) and appropriate use of in-office lead testing for venous blood samples. The device labeling contains information about the intended use of the device (including the test setting of use and the type of blood sample to use) and instructions for how to perform the test. Your letter also stated that capillary tests are the first blood lead level screening administered, and venous tests are often sent to a lab to confirm the initial diagnosis. Based on FDA's interactions with laboratories that perform lead testing, the type of sample used for initial testing and follow-up testing varies by individual practice.

[5] For instance, larger-capacity Clinical Laboratory Improvement Amendments (CLIA)-approved laboratories, such as reference labs, may use mass spectrometer and atomic absorption testing.

percentage of your patient results." At the time, Magellan did not send a copy of the Notice to Customers to FDA.

- In April 2015, Magellan submitted one medical device report (MDR) to FDA for the LeadCare Ultra, stating that the company had learned that the product may underestimate the amount of lead in some blood samples.[6] The company characterized the problem as a "malfunction" without any reported harm to patients and the subject of a "Class III recall."[7,8] Regarding potential risk from the observed malfunction, the MDR stated that implementation of a 24-hour processing delay would reduce the total level of risk from low to zero. The MDR also attached a copy of the company's November 2014 Notice to Customers, which characterized this possibility as an "infrequent occurrence" that "could impact a small percentage of your patient results."[9]

- Between September 29, 2014, and July 7, 2015, Magellan had another product that was undergoing premarket review by FDA, the LeadCare Plus. The LeadCare Plus is similar to the LeadCare Ultra, but the Plus test processes one sample instead of six samples at a time, costs less, and is generally intended for use by smaller labs.

    - During the review of the LeadCare Plus, Magellan failed to notify the FDA review team of the problem that Magellan had observed with the LeadCare Ultra, despite the fact that the review coincided with the company's Notice to Customers and subsequent MDR.

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[6] For a copy of the April 2015 MDR, see https://www.fda.gov/downloads/MedicalDevices/Safety/AlertsandNotices/UCM558970.pdf.

[7] Medical Device Reporting is one of the postmarket surveillance tools FDA uses to monitor device performance, detect potential device-related safety issues, and contribute to benefit-risk assessments of these products. It is a manufacturer's responsibility to monitor for potential problems with its device(s), perform a risk assessment when a potential problem is identified, determine the extent of risk and any appropriate actions, and submit any required report. Medical device manufacturers must submit MDRs to report deaths, serious injuries, and certain malfunctions. A device "malfunctions" when it fails to meet its performance specifications or otherwise perform as intended. For additional information about medical device reporting see https://www.fda.gov/MedicalDevices/Safety/ ReportaProblem/.

[8] A Class III recall is a voluntary correction or removal of a violative product that is not likely to cause any health problems or injury. A voluntary recall may be undertaken on the manufacturer or distributor's initiative, or at the request of FDA. Almost all recalls are conducted on a voluntary basis by the manufacturer. Under FDA regulations, a medical device firm is not required to report a Class III recall, although a firm may choose to do so. For additional information about medical device recalls, corrections, and removals, see: https://www.fda.gov/medicaldevices/deviceregulationandguidance/postmarketrequirements/recallscorrectionsandremovals/default.htm.

[9] Each year, FDA receives several hundred thousand medical device reports of suspected device-associated deaths, serious injuries, and malfunctions. The majority of MDRs submitted by firms are identified as malfunctions. For instance, in 2015, FDA received nearly 266,000 reports of serious injury or death and 600,000 malfunction reports. In the absence of reported patient harm, FDA's practice is to review malfunction reports for monitoring and trending purposes. Consistent with that practice, FDA reviewed the April 2015 MDR and determined that no follow-up was warranted. While reviewing information that has come to light during the Agency's current investigation, FDA found a lack of reliable data regarding the frequency and extent of inaccurate test results for the LeadCare testing systems and a lack of adequate effectiveness to support the mitigating steps taken by Magellan. It appears to FDA that Magellan repeatedly underestimated the risk to public health, such as in the April 2015 MDR.

- Magellan did not notify the FDA review team of the April 2015 MDR for the LeadCare Ultra.

- During the review, Magellan provided additional study data to support its submission for the LeadCare Plus, but the company did not explain that it had performed the additional studies with the 24-hour incubation period to address the performance problem with the test.

- During the review, Magellan amended the draft labeling for the LeadCare Plus to add an instruction for use regarding the 24-hour incubation period. Magellan did not identify this change as the result of an identified problem with the performance of the test. In a subsequent e-mail to the FDA reviewer, Magellan described the labeling changes as involving "minor updates."[10] It is not uncommon for sponsors to make minor changes to labeling during a premarket review.

- In November 2016, Magellan sent a Notice to Customers to inform them that falsely lower test results may occur when using venous blood on the LeadCare II testing system. The notice attributed the problem to use of some venous collection tubes, including the Becton Dickinson K_2-EDTA Vacutainer tubes, which, according to the notice, may introduce a sulfur-containing curing agent from the manufacture of the tubes' rubber stopper. The notice explained that "[w]hen a venous blood sample that may have been exposed to this substance is mixed with treatment reagent and analyzed immediately, the substance can suppress the lead response." In such cases, or when a customer would not know whether the blood sample had touched the tube's rubber cap, Magellan advised that customers implement a 24-hour delay in processing venous samples that had been collected at other sites and transported for testing. The notice stated that "[u]pon completion of further studies, we will update the package insert if necessary and provide you with any required documentation."

- In November 2016, Magellan attempted to submit a follow-up to the April 2015 MDR, which pertained to the LeadCare II testing system and the company's Notice to Customers about the 24-hour incubation period. The second MDR was also characterized by Magellan as a malfunction report.[11]

    - FDA learned about this MDR from our current investigation. In response to information requests to the company, FDA learned that Magellan attempted to submit the follow-up MDR in paper form. At the time, FDA had sent an automatic reply with instructions to submit the MDR electronically, per FDA's regulations that require electronic submission of MDRs. These regulations had

[10] Modifications to a test procedure are frequently done both before and after a diagnostic test is on the market. As a general matter, if pre-analytical sample handling and testing instructions are not followed closely by a laboratory, test results will be incorrect. As a result, Magellan's change to the instructions for use did not raise a concern to FDA review staff because the change was not identified as intended to mitigate a performance problem with the device.

[11] For a copy of the second MDR, see https://www.fda.gov/downloads/MedicalDevices/Safety/AlertsandNotices/UCM558973.pdf.

gone into effect in August 2015, with a compliance grace period until February 2016.

- FDA learned from our investigation that Magellan registered for an electronic submission account in February 2016 but never completed the process, in spite of assistance from the Agency.

- Magellan did not complete submission of the MDR until May 2017. Accordingly, it is referred to herein as the "May 2017 MDR."

- On March 3, 2017, Magellan submitted a "Special 510(k)" for the LeadCare Ultra and the LeadCare Plus to make certain changes to the tests.[12] The FDA review team identified several concerns while reviewing the information contained in the Special 510(k), including whether a Special 510(k) is appropriate for the types of changes requested.

  - As a result of FDA's inquiries to Magellan regarding the Special 510(k) submission, FDA's staff began its investigation as described here.

  - FDA's review of Magellan's data supporting the issues contained in its customer notifications did not confirm a root cause (including the blood collection tubes) for the inaccurate results. Rather, the Agency found that the company lacked reliable data identifying the root cause of the problem, the frequency and extent of inaccurate test results for the LeadCare Testing Systems, and effectiveness of the mitigating steps that had been taken (instructions regarding the incubation periods for the LeadCare Ultra and LeadCare II).

- In April, after discussions with FDA, Magellan initiated a recall of the LeadCare Testing Systems.

  - Initially, the company continued to assess the situation as warranting a lower-risk recall (Class III).

  - By the end of April, FDA determined that Magellan had significantly underestimated the risk to public health. Throughout early May, FDA worked with Magellan regarding the details of the recall, including that the situation warranted the most serious class of recall (Class I), that the recall would include all four LeadCare Testing Systems, and that Magellan would conduct the recall voluntarily.

- On May 17th, FDA issued its safety communication.[13]

  - FDA's safety communication explicitly stated: "Laboratories and health care professionals should follow recommendations in this Safety Communication

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[12] A Special 510(k) is available for certain changes to a device that do not affect the device's intended use or alter its fundamental scientific technology. Unlike a traditional 510(k), in which a manufacturer provides underlying performance data, the Special 510(k) relies on summary information regarding the manufacturer's design control activities.

[13] https://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/ucm558733.htm

rather than previous communications from Magellan Diagnostics on its LeadCare Test Systems, including Magellan's most recent Field Safety Correction Notification dated April 28, 2017." Magellan also confirmed that it shared the information from FDA's safety communication with its customers.

- In early June, FDA posted to its website information reflecting the Agency's formal classification of the recall for LeadCare and LeadCare II. This was an administrative action that did not reflect new information or otherwise change the information that had previously been communicated by FDA in the May 17th safety alert, which included all four LeadCare Testing Systems. Magellan distributed the May 17th FDA Safety Alert to its LeadCare and LeadCare II customers as part of this recall.

- In April, when FDA identified that the issue presented a risk to public health, FDA and CDC began collaborating to share information and to gain a mutual understanding of the potential impact of the problems observed with Magellan tests. FDA and CDC worked together to establish and issue the recommendations for laboratories, health care professionals, and at-risk individuals that were announced on May 17th.

- FDA and CDC have conducted joint outreach to consumer and health care groups, physician associations such as the American Academy for Pediatrics and the American Congress of Obstetricians and Gynecologists, and public health labs across the country to ensure they understand the scope of the problem and the resulting recommendations.

- FDA continues to investigate the root cause of the problem. Magellan had previously identified the interaction of the blood samples with the stopper of the vials of the venous blood collection tubes as the root cause. While we have not ruled this out, FDA does not have enough information to support it as a root cause at this time.

  - FDA and CDC are working together to carry out clinical studies to better understand the root cause of the problem. In May, CDC commenced a pilot project to evaluate LeadCare Testing Systems, with the objective to generate results that would inform development of a larger clinical study. A protocol for the clinical study is currently being developed. If and when a root cause is identified, FDA will work with Magellan and others as appropriate to help facilitate corrective actions to address that issue.

Additional Information in Response to the June 29th, 2017 Letter

Below is information about Magellan's products, next steps with respect to FDA's investigation, and FDA regulatory authorities that respond to additional questions included in your letter.

- **Medical device reports involving LeadCare Testing Systems**

In total, Magellan submitted six MDRs to FDA from 2004 through May 2017. Only two of the MDRs (the April 2015 MDR and the May 2017 MDR) addressed the issue of underestimation of blood lead levels due to some form of interference or lack of time of incubation. All six MDRs

were submitted as "malfunction" reports, and no serious injury or death reports were submitted for these devices.

Date FDA Received MDR	Device	Summary of MDRs Submitted by Magellan
2004	LeadCare	Low blood lead value (LeadCare – 38 µg/dL, reference lab value – 51µg/dL). After Magellan retested the instrument using control material, it determined the LeadCare system was operating within specification.
2010	LeadCare II	One customer reported an issue with blood lead patient samples trending higher than usual.
2011	LeadCare II	Customer reported problems with lead control material. After investigation, Magellan concluded that the root cause was the analyzer, not the lead controls. Liquid had been spilled on the analyzer and the spill left a residue inside the unit. Engineering review confirmed that the residue from the spill could cause the problem reported by affecting the potentials and sensor signals.
2013	LeadCare II	A customer was having trouble with frequent error messages. Magellan concluded the customer had not been using the LeadCare II blood lead testing system per the manufacturer's instructions for use. The customer was advised to retest any patients since the time the instrument was generating errors.
2015*	LeadCare Ultra	Increased frequency of false negative results on LeadCare Ultra device. Firm concluded risk was low and implemented a 24-hour incubation recommendation via customer communication letter.
2017*	LeadCare II	In a follow-up to the 2015 MDR, Magellan expanded the recommendation to include a 4-hour incubation step for the LeadCare II device to mitigate the potential for false negative results.

*These MDRs are related to the current investigation.

In addition, FDA's investigators included an observation related to MDR reporting in the Form 483 issued at the conclusion of the for-cause inspection of Magellan that concluded on June 29, 2017 (and which is discussed below). FDA is reviewing the inspection evidence related to this and other observations in the Form 483.[14]

[14] Form FDA 483 lists observations made by the FDA representative(s) during the inspection of a facility. These are inspectional observations and do not represent a final Agency determination regarding the facility's compliance.