FDA Executive Summary

Prepared for the
July 22, 2016 meeting of the
Clinical Chemistry and Clinical Toxicology Devices Panel
k153726
Afinion HbA1c Dx test system
Alere Technologies AS

Introduction

This document is the **FDA Executive Summary** for the meeting of the Clinical Chemistry and Clinical Toxicology Devices Advisory Panel meeting on the Afinion HbA1c Dx test system from Alere Technologies AS. The sponsor (Alere) has submitted a 510(k) (k153726) to add a diagnostic claim to their Afinion HbA1c assay. The Afinion HbA1c Dx assay is intended to be used in moderate complexity point-of-care (POC) settings as an aid in the diagnosis of diabetes and as an aid in identifying patients who may be at risk for developing diabetes. The submission is under review by the Division of Chemistry and Toxicology Devices (DCTD), Office of *In vitro* Diagnostics and Radiological Health (OIR), within the Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA).

This document will provide background on hemoglobin A1c (HbA1c), describe the current use of HbA1c *in vitro* diagnostic tests, and summarize the areas for which FDA seeks expertise and input from the Clinical Chemistry and Clinical Toxicology Devices Advisory Panel. Since current clinical guidelines recommend against the use of POC HbA1c test systems for the diagnosis of diabetes, FDA is seeking the panel's opinion on the suitability of the Afinion HbA1c Dx assay, and other future POC HbA1c tests submitted for this use, to diagnose diabetes in moderately complex laboratory settings. FDA is also requesting the panel's input on the sponsor's proposed plans to distinguish the new diagnostic Afinion HbA1c Dx assay from the existing Afinion HbA1c assay waived under Clinical Laboratory Improvement Amendments (CLIA) regulations, and whether these mitigations are sufficient to distinguish the waived version of this assay from the moderate complexity version. FDA also seeks the Advisory Panel's input on potential requests for CLIA waiver for diagnostic HbA1c POC tests.

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I. Rationale for Panel Meeting

In their "Standards of Medical Care in Diabetes" practice guideline (see Appendix A), the American Diabetes Association (ADA) began recommending the use of HbA1c for the diagnosis of diabetes in 2010. At that time, these guidelines stated that "POC assays [for HbA1c] are not sufficiently accurate at this time to use for diagnostic purposes." In 2013, the ADA revised the wording of the guidelines to state that "although [HbA1c] POC assays may be NGSP certified, proficiency testing is not mandated for performing the test, so use of these assays for diagnostic purposes could be problematic." The current version of the ADA Standards of Medical Care published in 2016 (Appendix A, S13) were further edited to state that "although point-of-care (POC) HbA1c assays may be NGSP certified, proficiency testing is not mandated for performing the test, so use of point-of-care assays for diagnostic purposes is not recommended."

POC testing typically refers to the use of an in vitro diagnostic test outside of a traditional central laboratory and near the site of patient care. Common POC test sites include physician office laboratories, emergency departments, operating rooms, intensive care units, outpatient clinics (e.g., diabetes clinics), and community health screenings (e.g., at events or fairs, big box store events, etc.) (Wagner EA, 2008). It is unusual for clinical practice guidelines to specify the type of laboratory setting necessary for a type of testing. FDA wishes to get further input from the clinical community, via our Advisory Panel, to determine whether the questions of safety and effectiveness that prompted these recommendations may be adequately addressed or mitigated to demonstrate that a POC HbA1c test could be substantially equivalent to other diagnostic tests for HbA1c. Because FDA was not present during the discussion that preceded the ADA guidelines, we do not know whether we understand the basis for the ADA's concerns about diagnosing diabetes in POC environments. For example, it is unclear whether the ADA's concern is specific to CLIA waived POC settings or also applies to moderately/high complex POC laboratories (see section V below). It is also unclear whether the concern with the lack of proficiency testing is the only concern that the ADA has with POC assays being used to diagnose diabetes. To facilitate discussion on this topic and to give the panel members the opportunity to ask clarifying questions, the agency has included the ADA on the agenda for this panel meeting to present their rationale for recommending against POC HbA1c assays to diagnose diabetes.

The sponsor's current submission is for a HbA1c test for use in moderately complex POC laboratories. However, the sponsor has informed FDA that, if this test is cleared, they are considering a future request for a CLIA waiver for this test system. Because proficiency testing is clearly a driving concern behind the ADA's recommendations and CLIA-waived laboratories are not subject to proficiency testing requirements, we would like input from

the panel on considerations/mitigations that may be necessary when FDA receives future requests for CLIA waiver for diagnostic HbA1c tests.

II. Overview of HbA1c

Glycated hemoglobin (including HbA1c) is formed in red blood cells by the non-enzymatic attachment of glucose to hemoglobin. Since the mid-1970s, the clinical community has recognized a direct relationship between HbA1c percentage and mean glucose concentrations over the preceding several weeks (Peterson KP, 1998). In general, higher percentages of HbA1c compared to total hemoglobin indicate poorer control of blood glucose levels. Today, clinicians routinely utilize *in vitro* diagnostic test results for HbA1c to diagnose pre-diabetes and diabetes, to gauge a patient's risk of developing diabetes in the future, and to assess a pre-diabetic or diabetic patient's glycemic control over time. Accurate HbA1c values are therefore critical for the correct diagnosis, risk assessment, and long-term monitoring of diabetes.

FDA currently regulates HbA1c tests for the following two general uses:

1. Diagnosis of diabetes and risk assessment of developing diabetes

   Since 2010, the American Diabetes Association (ADA) has endorsed *in vitro* diagnostic HbA1c test results as one of the clinical options for diagnosing diabetes in adult patients. Current ADA guidelines (see Appendix A, S14) establish the cut-off for positively diagnosing diabetes using glycated hemoglobin (HbA1c) at an HbA1c concentration of ≥ 6.5%. They state that for patients within an HbA1c range of 5.7–6.4%, it is reasonable to consider a diagnosis of pre-diabetes, and aggressive interventions and vigilant follow-up should be pursued for those patients considered at very high risk of developing diabetes (e.g., those with HbA1c >6.0%; Appendix A, S15). The ADA recommends that diagnostic HbA1c values should be confirmed without delay in a new blood sample using the same HbA1c test and that HbA1c tests used to diagnose diabetes should be performed in a laboratory using a method that is NGSP certified and standardized to the Diabetes Control and Complications Trial (DCCT) assay (Appendix A, S13).

   Several prospective studies that used HbA1c to predict the progression to diabetes demonstrated a strong, continuous association between HbA1c and subsequent diabetes. In a systematic review of 44,203 individuals from 16 cohort studies with a follow-up interval averaging 5.6 years (range 2.8–12 years), those with an HbA1c between 5.5–6.0% had a substantially increased risk of diabetes (5-year incidence from 9% to 25%). An HbA1c range of 6.0–6.5% had a 5-year risk of developing diabetes between 25% and 50% and a relative risk 20 times higher compared with an HbA1c concentration of 5.0% (Zhang X, 2010; Appendix A, S15).

2. Monitoring long-term glycemic control in patients with diabetes

In diabetic patients, higher HbA1c concentrations indicate a greater risk of developing diabetes-related complications (Albers JW, 2010; Stratton IM, 2000). Monitoring HbA1c in diabetic patients, for the purpose of assessing glycemic control and modifying therapy, may improve outcomes (Larsen ML, 1990). The American Diabetes Association (ADA) currently recommends performing HbA1c testing at least twice a year in patients who are meeting treatment goals and have stable glycemic control (Appendix A, S40). In patients whose therapy has changed or who do not exhibit good glycemic control, the ADA recommends more frequent HbA1c testing every three months (Jovanovic L, 2011). HbA1c testing alone may not be sufficient to determine glycemic control in certain patient groups (especially Type 1 diabetics and Type 2 diabetic patients with severe insulin deficiency), since it provides a more long-term overview of blood glucose levels and does not take into account the dynamics of glycemic variability. Therefore, the ADA encourages physicians to evaluate both HbA1c concentrations and self-measured blood glucose meter results when assessing a patient's level of glycemic control. Several POC HbA1c tests are available, and many consider POC tests to monitor HbA1c levels beneficial to patients as they provide the opportunity to discuss results with the patient during their appointment and, when needed, make more timely treatment changes (Appendix A, S40).

III. Regulation of HbA1c Assays

There are two separate FDA regulations pertaining to HbA1c tests. HbA1c tests intended for use in patients with diabetes to assess long-term glycemic control (commonly used for monitoring diabetes control) are regulated under the regulation 21 CFR 864.7470. These are Class II devices, which require 510(k) clearance prior to marketing.

Following the ADA's 2010 recommendation to use HbA1c test results for the diagnosis of diabetes and pre-diabetes, FDA evaluated the information they used to support this recommendation. The agency concluded that the clinical validity of this type of test was supported for this purpose by the information available in the public domain (e.g., prior clinical studies, peer-reviewed published data, etc.). However, at the time there was high variability in accuracy and precision of the HbA1c assays on the market for long-term monitoring of diabetes. While some of the widely available assays appeared to be accurate enough around clinical decision points to be used for the diagnosis of diabetes, FDA took into consideration that some available and future tests may not be accurate enough for this use. Therefore, FDA sought to create a regulatory distinction between assays that demonstrate sufficient analytical accuracy and precision to get a diagnostic claim, and those that are only FDA cleared for monitoring of long-term glycemic control. By doing

this, laboratories would be able to read the test labeling and determine whether a test had been assessed by the manufacturer and FDA for diagnostic use.

FDA developed recommendations for manufacturers on the analytical studies that should be done to demonstrate sufficient accuracy and precision for a diagnostic claim, including the appropriate design of precision, accuracy, and analytical specificity studies to demonstrate adequate performance within acceptable total error. FDA then worked with manufacturers who sought this claim, and in early 2013 the first test with this claim was authorized for marketing. With this de novo submission, FDA created a second, new regulation for HbA1c diagnostic test systems (21 CFR 862.1373). This regulation defines an HbA1c test system as a "device used to measure the percentage concentration of hemoglobin A1c in blood. Measurement of hemoglobin A1c is used as an aid in the diagnosis of diabetes mellitus and as an aid in the identification of patients at risk for developing diabetes mellitus." HbA1c test systems falling under this regulation are also considered Class II devices and require 510(k) clearance prior to marketing.

Because of the need for accurate and reliable diagnoses, FDA created certain "special controls" (i.e., requirements for tests under that regulation), with which all manufacturers who seek a diagnostic claim for their test must comply (Note: these are not requirements for HbA1c tests only intended for monitoring glycemic control in people already diagnosed with diabetes):

1. The device must have initial and annual standardization verification by a certifying glycohemoglobin standardization organization[1] deemed acceptable by FDA.

2. The premarket notification submission must include performance testing to evaluate precision, accuracy, linearity, and interference, including the following:

    a. Performance testing of device precision must, at a minimum, use blood samples with concentrations near 5.0 percent, 6.5 percent, 8.0 percent, and 12 percent hemoglobin A1c. This testing must evaluate precision over a minimum of 20 days using at least three lots of the device and three instruments, as applicable.

    b. Performance testing of device accuracy must include a minimum of 120 blood samples that span the measuring interval of the device and compare results of the new device to results of a standardized test method. Results must demonstrate little or no bias versus the standardized method.

[1] Currently, all diagnostic HbA1c tests are initially and annually certified by NGSP.

c. Total error of the new device must be evaluated using single measurements by the new device compared to results of the standardized test method, and this evaluation must demonstrate a total error less than or equal to 6 percent.

d. Performance testing must demonstrate that there is little to no interference from common hemoglobin variants, including Hemoglobin C, Hemoglobin D, Hemoglobin E, Hemoglobin A2, and Hemoglobin S.

3. When assay interference from Hemoglobin F or interference with other hemoglobin variants with low frequency in the population is observed, a warning statement must be placed in a black box and must appear in all labeling material for these devices describing the interference and any affected populations.

At the time of this panel meeting, the agency has cleared 221devices under the monitoring regulation 21 CFR 864.7470 (including several POC devices), and 8 devices under the diagnostic regulation 21 CFR 862.1373. There are currently no cleared diagnostic HbA1c assays intended for use at POC sites.

To obtain clearance of a new diagnostic HbA1c test, sponsors submit data that complies with the special controls (requirements) listed above for FDA review (for more details about the agency's review process for HbA1c assays, please see Appendix C). FDA then determines whether the sponsor has adequately met the special controls, and also whether the new device is substantially equivalent to the predicate (see http://www.accessdata.fda.gov/cdrh_docs/reviews/K121610.pdf for an example of a summary of the data used for clearance of a diagnostic HbA1c assay).

Alere has chosen to include a summary of the analytical data they plan to use to support clearance of their device in their executive summary. Please not that some of the performance data included in the sponsor's meeting materials has not yet been submitted to, or reviewed by, FDA.

FDA is currently evaluating whether or not the analytical performance of the Afinion HbA1c Dx assay (see Section IV below for additional description of this test) is substantially equivalent to other tests with this intended use, and also whether the sponsor has adequately met the special control requirements for this type of assay. As for any 510(k) submission, if the data submitted do not demonstrate substantially equivalent accuracy and reliability for this test, FDA will not clear it for marketing. The discussion at this panel meeting should focus on the questions related to POC use and CLIA waiver. FDA therefore requests that, for the purposes of this discussion, the panel assume that the Afinion HbA1c Dx assay has equivalent analytical performance to other cleared diagnostic HbA1c tests.

IV. Afinion HbA1c Dx Test System

In k153726, the sponsor has proposed a new device, the Afinion HbA1c Dx test system (Afinion HbA1c Dx assay, AS100 analyzer, Afinion HbA1c controls), which is intended to be used in moderate complexity POC settings for the quantitative determination of glycated hemoglobin (HbA1c) in capillary (fingerstick) and venous whole blood as an aid in the diagnosis of diabetes and as an aid in identifying patients who may be at risk for developing diabetes.

Although the device as presented in k153726 is intended for use in moderate complexity POC laboratories only, the sponsor has informed FDA that they are considering seeking CLIA-waived status for the Afinion HbA1c Dx device in the future.

1. Device Description

   The Afinion HbA1c Dx is a fully automated boronate affinity assay for the determination of the percentage of HbA1c in capillary and venous whole blood. The Afinion HbA1c Dx assay is intended for use with the Afinion AS100 Analyzer and Afinion HbA1c Controls. For more information, please see the sponsor's proposed labeling in Appendix B.

   The test begins with a whole blood sample collected with the integrated sampling device before the test cartridge is placed in the cartridge chamber of the Afinion AS100 Analyzer. The sample is then automatically diluted and mixed with a solution that releases hemoglobin from the erythrocytes. After the hemoglobin is precipitated, the sample mixture is transferred to a blue boronic acid conjugate which binds to the cisdiols of glycated hemoglobin. This reaction mixture is soaked through a filter membrane and all precipitated hemoglobin, conjugate-bound and unbound (i.e. glycated and nonglycated hemoglobin) remains on the membrane. Excess conjugate is removed with a washing reagent. The analyzer measures the reflectance of the precipitate on the membrane as blue (glycated hemoglobin) and red (total hemoglobin) color intensities. The analyzer calculates a ratio proportional to the percentage of HbA1c in the sample and displays as the % HbA1c.

2. Device History

   The Afinion HbA1c Dx is a modification of an existing device, the Afinion HbA1c test system (Afinion HbA1c assay, AS100 analyzer, Afinion HbA1c controls), which was cleared by FDA in 2005 for the long-term monitoring of HbA1c in people with diabetes (k050574). The Afinion HbA1c test system was CLIA waived by application in 2006

and can be used in CLIA waived settings, in moderate complexity POC settings, and in central laboratory settings.

Since the initial clearance, the Afinion HbA1c assay has been modified twice. In 2011, the sponsor added a data accessory to allow the transfer of test results to a laboratory information system (k110056), and in 2015, the sponsor changed the capillary blood collection device material from glass to plastic (k151809). In addition to HbA1c, the AS100 analyzer was cleared in 2008 and 2014 as part of other test systems that measure Total Cholesterol, HDL Cholesterol, Triglycerides, Creatinine, and Microalbumin (k072409, k132031). Contrary to the Afinion HbA1c test system, these other tests cleared for use on the AS100 analyzer are not CLIA waived and are for use in moderate complexity POC laboratories only.

The table below shows a comparison of the similarities and differences between the cleared and CLIA-waived Afinion HbA1c test system and the Afinion HbA1c Dx test system described in the current submission (k153726):

	Similarities and Differences
	Waived Afinion HbA1c test system (cleared in 2005) vs. **New Afinion HbA1c Dx test system** **(proposed CLIA moderate complexity)**
Reagent	• Both devices use identical reagents in the same formulation • Differences between the reagent cassettes for each device: - the barcode that identifies the test - the catalog number - the name of the reagent

	Similarities and Differences
	Waived Afinion HbA1c test system (cleared in 2005) vs. **New Afinion HbA1c Dx test system** **(proposed CLIA moderate complexity)**
Analyzer	• The name of the analyzer is the same for both devices – "Afinion AS100 Analyzer" • The analyzer processes the reagents and samples, and calculates the %HbA1c results, in the same way for both devices • Although the analyzer for both systems is the same instrument with the same name, there would be two separate catalog numbers for two versions of the Afinion AS100 Analyzer: - Non-waived laboratories could buy a version of the Afinion AS100 Analyzer that would be capable of running all tests on the Afinion test menu, including the new Afinion HbA1c Dx test - CLIA waived laboratories that use the Afinion HbA1c test system (including the current installed customer base) would have instruments with the following software features: ▪ If a non-CLIA waived cartridge is inserted, the analyzer will not perform a test and instead display the following: "*The Analyzer is configured for CLIA waived tests only. See CLIA Statements on page 2 [of the user manual] for further information. Contact your local supplier for assistance"* ▪ At start up, the screen will display "CLIA waived" - Both the waived and moderate complexity versions of the Afinion AS100 Analyzer would have quality control lockout functionality to restrict operators and tests
Labeling	• The waived Afinion HbA1c and moderate complexity Afinion HbA1c Dx reagent cassettes would be shipped with different package inserts • A quick guide accompanies the Afinion AS100 analyzer. This quick guide would be specific to the CLIA waived or moderate complexity analyzer version. • Both analyzer versions would have the same user manual
Results	• The CLIA waived Afinion HbA1c test system displays results to one decimal point • The new Afinion HbA1c Dx test system displays results to two decimal points

V. Clinical Laboratory Improvement Amendments (CLIA)

The Centers for Medicare & Medicaid Services (CMS) regulate all clinical laboratory testing in the United States via the Clinical Laboratory Improvement Amendments of 1988 (CLIA). The objective of the CLIA program is to ensure quality laboratory testing, i.e. to provide patients with reliable, accurate, and timely in vitro diagnostic test results.[2] Any laboratory that performs testing on human specimens, such as blood, body fluid, and tissue, for the purpose of diagnosis, prevention, or treatment of disease, or assessment of health, must be certified under the CLIA regulations.[3]

Since November 13, 2003, CMS has delegated the authority to FDA to assign all *in vitro* diagnostic tests to one of three complexity categories under CLIA[4]:

1. Waived tests – simple, accurate methodologies with a low likelihood of erroneous results by the user which pose no unreasonable risk of harm to patients if performed incorrectly. Certain types of tests are waived automatically (e.g., urine pregnancy tests, visually read urine dipsticks, etc.).[5] In addition, all tests that are cleared or approved for home use or for over-the-counter use are waived (FDA Guidance "Administrative Procedures for CLIA Categorization[6]). Finally, manufactures may apply (see below) for waived status by demonstrating, using data and other information, that the test meets the statutory criteria for waiver (i.e., is simple, with a low likelihood of an erroneous result).

2. Moderate complexity tests – These tests may include several operator steps (such as separation of a blood sample into serum or plasma), are usually automated, and require a moderate level of expertise from the laboratory personnel to run and maintain them (e.g., automated immunoassays or electrolyte tests run on large clinical chemistry analyzers). Labs that run moderate complexity tests are required to participate in proficiency testing programs (see below).

3. High complexity tests – These are complex tests that require a high level of operator expertise and training and may require extensive troubleshooting and/or several manual operator steps (e.g., mass spectrometry or next generation DNA sequencing). In addition, any test which is not CLIA categorized or is modified by the laboratory (e.g., a cleared or approved test that is modified) is by default a high complexity test.

[2] https://www.cms.gov/Regulations-and-Guidance/Legislation/CLIA/index.html?redirect
[3] https://wwwn.cdc.gov/clia/Regulatory/default.aspx
[4] https://www.cms.gov/Regulations-and-Guidance/Legislation/CLIA/Categorization_of_Tests.html
[5] So-called "waived by regulation"- 21 CFR 493.15
[6] http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070889.pdf

Approximately 251,000 laboratories in the United States are currently covered by CLIA regulations.[7] Laboratories performing only waived tests are subject to minimal regulation. Laboratories performing moderate or high complexity tests must comply with specific laboratory standards governing certification, personnel, proficiency testing, patient test management, quality assurance, and quality control. The table below describes the main similarities and differences between waived, moderate, and high complexity laboratories (please note that certain requirements may vary by state):

	Certificate of Waiver	**Moderate complexity**	**High complexity**
Proficiency Testing	Not required	Required, 3 times/year	Required, 3 times/year
Personnel requirements	None	Laboratory Director (advanced degree) Technical Consultant Clinical Consultant Testing Personnel (at least high school degree with experience)	Laboratory Director (advanced degree and board-certified) Technical Supervisor Clinical Consultant (advanced degree) General Supervisor Testing Personnel (at least lab science or medical technology associate degree)
Quality Control (QC) and Quality Assessment (QA) Program Requirements	Not required. Waived labs only need to follow manufacturer's QC instructions in the labeling.	Yes	Yes

[7] https://www.cms.gov/Regulations-and-Guidance/Legislation/CLIA/index.html?redirect

	Certificate of Waiver	Moderate complexity	High complexity
Inspection Frequency by CMS	On-site visits for ~2% of laboratories each year	Biennial, on-site	Biennial, on-site

VI. Point-of-care (POC) testing

As stated above, POC testing typically refers to the use of an *in vitro* diagnostic test outside of a traditional central laboratory and near the site of patient care. Common POC test sites include physician office laboratories, emergency departments, operating rooms, intensive care units, outpatient clinics (e.g., diabetes clinics), and community health screenings (e.g., at events or fairs, big box store events, etc.) (Wagner EA, 2008). CLIA waived tests are predominantly POC tests, but not all POC tests are CLIA waived tests. Many POC settings are moderate complexity certified laboratories.

Those who are advocates for POC HbA1c testing emphasize the advantage of having access to accurate tests while patients are interacting with their healthcare providers. Multiple studies have shown that POC HbA1c testing offers substantial benefits to patients by making testing more accessible and therefore providing an opportunity for more timely treatment changes, leading to increased glycemic control [Appendix A, S40; (Lenters-Westra E, 2010; Cagliero E, 1999; Ferenczi A, 2001; Miller CD, 2003). Clinicians are able to discuss test results with patients before they leave the appointment, which can be particularly beneficial in populations where patients may not be likely to return for follow-up care.

In contrast, those who oppose POC HbA1c testing raise concerns about the accuracy and reliability of the testing. In CLIA waived POC settings, tests may be performed by anyone. In some CLIA waived settings, users without any laboratory training (e.g., volunteers, administrative personnel) perform the testing. In other settings, such as physician offices, nurses or nursing assistants may perform the tests. In moderate complexity POC laboratories, tests are performed under the oversight of a qualified laboratory medical director with requirements for personnel training and proficiency testing (Wagner EA, 2008). It has been reported that the likelihood of obtaining and reporting inaccurate HbA1c test results in POC settings is directly related to the competency of the staff performing the test (Weykamp C, 2013). The more expertise laboratories have, the more likely they are to recognize inaccurate test results and to identify possible causes for such results (e.g., interferences, user error, etc.). In addition, there is evidence in the literature that test-related variability leading to systematic or random bias in HbA1c values may be especially prevalent in POC devices (Weykamp C, 2013). In a recent study, test results obtained with

the two most commonly used POC HbA1c test methods, the Alere Afinion HbA1c and the Siemens DCA Advantage, were compared to results obtained by central laboratory methods as well as CAP survey test results over a three year period. Despite high correlations among the POC techniques and within-range performance for control material, both assays showed significant variability (positive and negative drift) compared to centralized laboratory method results as well as CAP survey samples over the duration of this study (Paknikar S, 2016). Finally, based on data comparing POC HbA1c test results to a standardized method, the authors of several studies caution physicians to be careful not to rely on POC HbA1c testing alone to evaluate the quality of long-term glucose control in diabetic patients (Lenters-Westra E, 2014a; Paknikar S, 2016). Two separate articles propose that measurements of HbA1c should be confirmed by a laboratory method at least once a year and call for mandatory proficiency testing for users of POC HbA1c assays to ensure ongoing quality (Lenters-Westra E, 2014a; Leca V, 2012).

We ask the members of this Advisory Panel to consider both the potential benefits of POC HbA1c diagnostic testing, as well as the potential risks.

VII. Proficiency Testing

Proficiency testing is one of the elements of the CLIA program implemented in moderate and high complexity laboratories to ensure ongoing quality. Proficiency testing is the testing of unknown samples sent to a laboratory by a CMS approved proficiency testing program. Most sets of proficiency testing samples are sent to participating laboratories three times per year. After testing the proficiency testing samples in the same manner as a patient specimen, the laboratory reports its sample results back to their proficiency testing program. The program grades the results using the CLIA grading criteria and sends the laboratory scores reflecting how accurately it performed the testing compared to other similar laboratories. CMS and accreditation organizations routinely monitor their laboratories' performance. Routine reviews of proficiency testing reports by the laboratory staff and director will alert them to areas of testing that are not performing as expected and also indicate subtle shifts and trends that, over time, would affect their patient results.[8]

For HbA1c, CLIA regulations require that moderate complexity laboratories offering HbA1c testing verify the accuracy of their test(s) at least twice annually. Laboratories can choose to participate in a voluntary proficiency testing program (such as the CAP survey, described below) or to compare their test results to those of another laboratory for the same patient samples.

[8] https://www.cms.gov/Regulations-and-Guidance/Legislation/CLIA/downloads/CLIAbrochure8.pdf

The CAP survey is a voluntary biennial proficiency testing program established by the College of American Pathologists (CAP). The CAP program intends to provide information about accuracy and precision when HbA1c assay methods (both POC and laboratory-based) are used in clinical and realistic environments, including any potential influence caused by end-users. In the CAP program, three to five pooled, fresh whole-blood reference samples consistent with low, medium, and high HbA1c levels are mailed to participating individual clinical laboratories, which then analyze them in the same manner they would patient samples and return the results to CAP. Target values for each whole blood sample are assigned by the mean result of all standardized reference laboratories in the NGSP network. Two out of the three samples must demonstrate accuracy within ± 6% of the NGSP target values for any assay methods to pass the CAP survey. The survey reports each assay's mean % HbA1c, mean bias to the NGSP reference value, and coefficient of variance (CV) as it relates to inter-laboratory imprecision. Although the CAP survey does not specify any acceptance criteria for precision and accuracy, it does recommend a mean bias of <0.2 % and a CV ≤ 3.5% (preferably <2%) while noting that less acceptable assay methods are those with a mean bias of >0.3 % and CV >4% (www.ngsp.org; Goodall I, 2007; Whitley HP, 2015).

Although the CAP survey is a very useful tool to evaluate and compare accuracy and inter-laboratory precision of HbA1c methods in a realistic clinical environment, there are several drawbacks to the CAP survey that are specific to POC HbA1c tests:

1. Users of point-of-care HbA1c devices who participate in the CAP survey may not be representative of most users of these devices. Participating sites are more likely to be associated with a CAP-accredited laboratory and have more experienced testing personnel (Little RR, 2014). Smaller moderate complexity POC laboratories and CLIA waived POC settings, which are not subject to mandatory proficiency testing and employ lesser trained users, may be less likely to participate in the CAP program, or other proficiency testing programs, in a voluntary fashion.

2. The number of users participating in the CAP survey differs greatly for the various HbA1c testing methods. For at least some of the POC HbA1c test systems, there may not be enough supporting proficiency testing data available to obtain significant insights into the assays' real-world performance (Little RR, 2014).

3. The CAP survey only evaluates HbA1c test performance for venous whole blood specimens. The program does not assess accuracy or precision in capillary blood samples, although some of the test methods are FDA cleared for use with this sample matrix (including the Afinion HbA1c). In FDA's experience, test results from capillary blood samples tend to be more variable (lower accuracy and precision) than venous whole blood test results.

VIII. CLIA Waiver

The sponsor's current submission is for an HbA1c test for use in moderately complex POC laboratories, and the information above is intended to provide background discussion to inform the Advisory Panel members' deliberation and recommendations on the questions relating to moderate complexity POC claims for this diagnostic HbA1c test.

As stated in section I, the sponsor has informed FDA that, if this test is cleared, they are considering a future request for CLIA waiver for this test system. This section is intended to provide some additional information on the mechanism for obtaining CLIA waived status for a test like this one, so that FDA may obtain the Advisory Panel's input on potential future requests for CLIA waiver for diagnostic HbA1c POC tests.

Manufactures may apply for waived status by demonstrating, using data and other information, that the test meets the statutory criteria for waiver (i.e., is simple, with a low likelihood of an erroneous result). The FDA guidance "Recommendations for Clinical Laboratory Improvement Amendments of 1988 (CLIA) Waiver Applications for Manufacturers of In Vitro Diagnostic Devices"[9] recommends approaches for manufacturers to demonstrate that a device is simple and accurate and can be categorized by FDA as "waived." The following are examples of FDA recommendations for sponsors applying for a CLIA waiver for their device:

1. Sponsors applying for a CLIA waiver should describe how and why their device is simple, i.e. easy for untrained users to operate correctly in a non-laboratory setting. CLIA waived devices are commonly fully automated, require no user intervention during sample analysis (e.g., no centrifugation of samples, no complex addition of multiple reagents, no need for specialized equipment, etc.), and allow for easy and straight-forward interpretation of test results and error messages.

2. Sponsors should assess all potential ways that their device could produce a false test result, including user errors, component malfunctions, and environmental influences (e.g., temperature/humidity, lighting, etc.). In addition to identifying potential sources of error, sponsors should provide validation data to show that their device includes effective fail-safe mechanisms and alerts (e.g., quality control, operator lock-out function, error messages, etc.), which avoid or minimize the risk that untrained users in a typical CLIA waived environment could obtain a false test result. For example, an effective fail-safe mechanism may detect certain conditions that may produce an

[9] http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070890.pdf

inaccurate result (e.g., too much or too little sample applied) and produce an error code in lieu of a potentially inaccurate result.

3. The instructions for use should include a quick reference guide in addition to full instruction for use and should be written at no higher than a 7th grade reading level. A quick reference guide is typically an abbreviated (e.g., one page) version of the instructions for running the test. Sponsors should demonstrate that untrained users in CLIA waived settings can comprehend the test instructions and use them to successfully operate the device.

4. Sponsors should provide data to demonstrate that untrained users can obtain accurate test results in real-life CLIA waived settings. This is achieved by specific types of clinical studies that vary in design depending on the type of test (i.e., qualitative vs. quantitative results). The study typically includes at least 360 patient samples, of which no more than 120 may be contrived or archived samples. Samples should be collected and tested by at least nine untrained users over a minimum of two weeks. For HbA1c assays, test results from the new device would typically be compared to HbA1c values obtained by an NGSP-certified laboratory method, and at least 95% of test results should fall within a clinically acceptable total error zone.

IX. Summary of Post-market Safety for HbA1c devices

1. Medical Device Reports

   FDA performs surveillance activities to identify and track adverse events associated with devices that are on the market.

   Since the first diagnostic HbA1c assay was cleared in 2013, FDA has received 16 medical device reports (MDRs) for this type of device (eight diagnostic HbA1c tests have been cleared to date). Most of the MDRs reported inaccurate (falsely elevated or decreased) test results due to malfunction of the device or user error. There have been no reports of injury to a patient as a result of inaccurate HbA1c test results.

   In comparison, FDA received 454 MDRs for the approximately 38 HbA1c tests indicated for long-term monitoring control that were marketed in the U.S. during the same time frame. Similar to the MDRs reported for diagnostic HbA1c assays, MDRs about monitoring HbA1c assays were mostly related to inaccurate test results due to malfunction of the device.

Please note that because users may not always identify incorrect test results, and also may not identify incorrect results as an "adverse event," MDRs for *in vitro* diagnostic tests are extremely underreported.

Alere has not reported any MDRs for the Afinion HbA1c test system.

2. Recalls

Since 2013, there have been no recalls for diagnostic HbA1c assays and 12 Class II (moderate risk) recalls for monitoring HbA1c assays. There have been no recalls for the Afinion HbA1c test system.

X. Panel Questions

FDA wishes to get further input from the clinical community, via our Advisory Panel, to determine whether the concerns that prompted the ADA to recommend against the use of POC HbA1c tests for diabetes diagnosis, may be adequately addressed or mitigated. In addition, though the sponsor's current submission is for a HbA1c test for use in moderately complex POC laboratories, if this test is cleared, the sponsor is considering a future request for a CLIA waiver for this test system. Because proficiency testing is clearly a driving concern behind the ADA's recommendations and CLIA-waived laboratories are not subject to proficiency testing requirements, we would like input from the panel on considerations/mitigations that may be necessary when FDA receives future requests for CLIA waiver for diagnostic HbA1c tests.

We have the following discussion questions for the panel to address during the Advisory Committee Meeting.

1. In their "Standards of Medical Care in Diabetes" practice guidelines, the American Diabetes Association recommends against the use of POC HbA1c tests for the diagnosis of diabetes.

    a. Does the panel have any concerns about risks to health regarding the use of POC HbA1c devices in general for the diagnosis of diabetes? If so, please describe these concerns.

    b. Does the Afinion HbA1c Dx test system, with an intended use in moderate complexity POC settings, raise any new concerns about risks to health? If so, please describe these concerns.

    c. If the panel has concerns about risks to health for a or b above, what mitigations, if any, may be implemented to address those concerns?

2. The sponsor has proposed a number of ways to separate their CLIA waived HbA1c test from their moderately complex diagnostic HbA1c test. However, laboratories in the clinical community will be aware that the Afinion HbA1c Dx reagent and the Afinion HbA1c reagent are the same test with two different names.

    Is the sponsor's proposed strategy to differentiate the CLIA waived Afinion HbA1c test system from the Afinion HbA1c Dx test system adequate to address concerns about the use of POC HbA1c tests to diagnose diabetes in CLIA waived settings?

3. Based on the design of the Afinion HbA1c Dx test system:

    a. Please discuss the potential advantages and disadvantages of using this test as an aid in the diagnosis of diabetes and as an aid in identifying patients who may be at risk for developing diabetes in CLIA waived point-of-care settings?

    b. If there are any risks to health associated with the use of this device in CLIA waived point-of-care settings, are there potential mitigations that may be employed by the manufacturer that are adequate to address these risks to health?

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