CLIA Waiver by Application Approval Determination

Decision Summary

A. Document Number

CW200005

B. Parent Document Number

k200788

C. CLIA Waiver Type:

Dual 510(k) and CLIA Waiver by Application (Dual Submission)

D. Applicant

Arkray, Inc.

E. Proprietary and Established Names

Assure Titanium Blood Glucose Monitoring System

F. Measurand (analyte)

Glucose

G. Sample Type(s)

Fresh capillary fingertip whole blood

H. Type of Test

Quantitative amperometric assay (glucose oxidase)

I. Test System Description

1. Overview

The Assure Titanium Meter Blood Glucose Monitoring System consists of a hand-held, battery powered meter, disposable test strips and control solutions for use as an aid to measure glucose concentration in blood. It utilizes biosensor technology for the quantitative determination of glucose concentrations in fresh capillary whole blood samples. Glucose in the blood reacts with the reagent in the test strip, and this produces a small electric current (amperometry). The strength of this current is proportional to the

concentration of glucose in the blood. The meter measures this current and calculates the patient's glucose level.

2. Test System Components

The Assure Titanium Blood Glucose Monitoring System includes the following components:

- Assure Titanium Blood Glucose Meter
- Assure Titanium Blood Glucose Test Strips
- Assure Control-Control Solutions (3 levels)
- Quick Reference Guide (QRG), User Manual, Test Strips Package Insert
- Batteries

Assure Titanium Blood Glucose Test Strips and Assure Control-Control Solutions are available for purchase separately.

J. Demonstrating "Simple"

- The Assure Titanium Blood Glucose Monitoring System consists of the fully automated Assure Titanium Blood Glucose Meter and single use Assure Titanium Blood Glucose Test Strips.

- The Assure Titanium Blood Glucose Monitoring System uses direct, unprocessed whole blood samples and requires no specimen manipulation before performing the test.

- There is no reagent handling. Reagents are secured within the test strip. Once the test strip is inserted into the meter the sample is applied directly to the test strip and the test result is displayed. There are no further procedural steps.

- The Assure Titanium Blood Glucose Monitoring System provides direct readout of quantitative results that require no interpretation, or calculation by the operator.

- The Assure Titanium Blood Glucose meter does not require calibration or coding by the user. The detection of the calibration code is automatic.

- The Assure Titanium Blood Glucose Monitoring System requires no operator intervention during the analysis steps.

- The Assure Titanium Blood Glucose Monitoring System requires no technical or specialized training with respect to troubleshooting or interpretation of multiple or complex error codes. Error messages are unambiguous and include easy-to-interpret solutions.

- The Assure Titanium Blood Glucose Monitoring System requires no electronic or mechanical maintenance. Maintenance consists of external cleaning and disinfection of the instrument.

- The Assure Titanium Blood Glucose Monitoring System includes a Quick Reference Guide (QRG) that includes troubleshooting information with simple error code descriptions.

K. Demonstrating "Insignificant Risk of an Erroneous Result"- Failure Alerts and Fail-Safe Mechanisms

1. Risk Analysis

   A comprehensive risk analysis was conducted for the Assure Titanium Blood Glucose Monitoring System to assess the risks of providing the incorrect patient results and the safety risks to the patient or operator associated with the operation of the system and to demonstrate that the system is robust to known sources of error. All risks of harm to the patient or operator were mitigated to an acceptable level, and the system was demonstrated to be robust to known sources of error.

2. Fail-Safe and Failure Alert Mechanisms

   a. Failure alerts (error messages) and fail-safe mechanisms (lockout functions)

   The system will provide an error message, or a lockout function will occur and will not allow output of test results for the following conditions:
   - **EE**: if the battery has been replaced, error message EE and the message "RESET" will be displayed. The user is advised to press "M" to enter set-up mode and verify that date and time are correct.
   - **E0**: if a blood sample is measured during QC lock, error message E0 will be displayed. The user is advised to remove the used test strip and perform control solution test with a new test strip.
   - **E1**: if the contact bars of the test strip are dirty, a used test strip is inserted into the meter or a different type of test strip is inserted into the meter, error message E1 and a test strip icon will be displayed. The user is advised to repeat the test with a new test strip.
   - **E2**: if there is a problem inside the meter, error message E2 will be displayed. The user is advised to Contact ARKRAY Technical Customer Service.
   - **E3**: if the confirmation window is not filled because of abnormal viscosity or insufficient volume, error message E3 will be displayed. The user is advised to repeat the test with a new test strip.
   - **E4**: if the battery is low, error message E4 and a battery icon will be displayed. The user is advised to replace the battery.
   - **E5**: if an abnormal sample has been detected, the contact bars of the test strip are dirty or an incorrect sample type was used, error message E5 will be displayed. The user is advised to use a new test strip and repeat measurement with fresh capillary whole blood sample drawn from the fingertip.
   - **E6**: if the environment is outside 46°F to 104°F (8°C to 40°C), error message E6 and a thermometer error icon will be displayed. The user is advised to leave the meter and test strips somewhere where the temperature is 46-104°F (8-40°C) and

relative humidity is 10-90 % for at least 30 minutes, before conducting a measurement.

- **E7**: if there is a problem with the measurement unit of the meter, error message E7 will be displayed. The user is advised to Contact ARKRAY Technical Customer Service.
- **E8**: if there is a problem with the communications unit of the meter, error message E8 will be displayed. If this error message appears frequently, the user is advised to Contact ARKRAY Technical Customer Service.
- **E9**: if the meter cannot detect the surrounding temperature correctly, error message E9 and a thermometer icon will be displayed. The user is advised to Contact ARKRAY Technical Customer Service.
- **'Hi'**: is displayed when the glucose test result is greater than 600 mg/dL.
- **'Lo'**: is displayed when the glucose test result is less than 10 mg/dL.

b. External control materials

i. The use of external quality control materials is recommended to demonstrate that the Assure Titanium Blood Glucose Meter and Assure Titanium Blood Glucose Test Strips are working properly. The labeling states that user should perform quality control testing only with the Assure Control-Control Solutions.

ii. The frequency of running quality controls is stated in the labeling.

Three different levels of Assure Control- Control Solutions are available. It is recommended to run at least Control Solution Level 2 and Level 3:

- Before using a new meter or new vial of test strips
- Every 24 hours to avoid QC lockout
- During the following circumstances:
  - Each new operator
  - Whenever there is an indication that the meter or test strips are not working properly.
  - The meter has been dropped or damaged.
  - The test results do not reflect how the patient feels.
  - The results appear to be abnormally high, low, or are not consistent with the patient's clinical symptoms.

iii. Directions for use are clearly stated in the labeling (QRG, user manual and test strip insert).

iv. Storage and stability are stated in labeling. The user should follow the manufacturer's instructions for storage and stability.

v. Three levels of ready-to-use liquid control solutions are available for use (Level 1, Level 2, Level 3).

vi. Manufacturer: ARKRAY

3. Flex Studies

Based on the risk analysis and the identification of potential errors, the following flex studies were conducted on the Assure Titanium Blood Glucose Monitoring System to demonstrate that the test system is robust when its operational limits are stressed due to potential operator errors, factors affecting specimen or test system integrity, or environmental factors. The studies were conducted using the Assure Titanium Blood Glucose Meter and Assure Titanium Blood Glucose Test Strips:

a. Environmental Factors

i. System Operating Conditions Testing:

To assess the performance of the Assure Titanium Blood Glucose Monitoring System when used under various operating temperature and humidity conditions, the system was tested at four different temperature and humidity conditions including low temperature/low humidity (8°C/10% RH), low temperature/high humidity (8 °C/90% RH), high temperature/low humidity (40°C/10% RH) and high temperature/high humidity (40°C/90% RH). Each of 3 venous whole blood glucose levels (55-77, 114-144 and 316-356 mg/dL) were tested by 10 meters, using 3 lots of test strips, for a total of 10 replicates per sample, per condition. Values measured by the Assure Titanium Blood Glucose Monitoring System were compared to the comparator method (YSI 2300 STAT Plus). The results of the study demonstrate that accurate test results can be obtained when the system is operated at 8-40°C (46-104°F) and 10-90% RH.

ii. Altitude Effects:

A simulated high-altitude study was conducted in a pressure chamber to simulate the effects of sea level (<500 ft) and high-altitude (10,000 ft) on the Assure Titanium Blood Glucose Monitoring System. Venous whole blood samples adjusted to 3 glucose concentrations (55-77, 114-144 and 316-356 mg/dL) were tested in replicates of 10, using 10 meters and 3 lot of test strips, for a total of 30 replicates per sample, per condition. Values measured by the candidate device were compared with the glucose measurements obtained from the comparator method (YSI 2300 STAT Plus). The results of the study demonstrate that accurate test results can be obtained when the system is operated at altitudes of up to 10,000 ft (3,048 meters).

b. Reagent Integrity

Test Strip Stability Testing:

Shelf-life and open vial stability of the Assure Titanium Blood Glucose Test Strips were previously evaluated in k170064 using whole blood samples and were found to support the claimed shelf-life of 24 months and open vial stability of 6 months when stored at 34-86°F (1-30°C) and 10-90% relative humidity.

c. Operator Error/Human Factors

i. Sample Volume Study:

A study was conducted to support the claimed minimum sample volume of 0.5 µL for the Assure Titanium Blood Glucose Monitoring System. Venous whole blood samples at 3 glucose concentrations (50-65, 100-120 and 200-250 mg/dL) were tested at 6 sample volumes (0.1, 0.3, 0.5, 1.0 and 5.0 and 10.0 µL) using 3 lots of test strips. Values obtained were compared to the comparator method (YSI 2300 STAT Plus). The results of the study demonstrate that accurate test results can be obtained with a minimum sample volume of 0.5 µL. The meter has an error message displayed if enough blood is not added to the test strip. This feature was validated and was shown to function as intended.

ii. Sample Perturbation Study:

A sample perturbation study was conducted to assess the effect of events such as wicking away of blood from the test strip, flicking the test strip, or flicking of the meter during the start of the measurement on the Assure Titanium Blood Glucose Monitoring System. Venous whole blood samples at 3 glucose concentrations (50-65, 100-120 and 200-250 mg/dL) were tested using 3 lots of test strips, in replicates of 10 per lot, when performing each of following perturbation methods:

- Flick the strip by pressing strip down at a comer with a finger until it almost touches the counter-top and quickly release.
- Flip the meter on to its side (left or right) and release.
- Wick the sample by dabbing the end of the strip with a tissue.

Values obtained were compared to the comparator method (YSI 2300 STAT Plus). The results of the study demonstrate that the Assure Titanium Blood Glucose Monitoring System is robust to sample perturbation.

iii. Intermittent Sampling:

An intermittent sampling study was conducted to assess the effect of an event when a short sample (0.25 µL) is applied to a test strip, a glucose measurement begins, and the user adds more sample (0.25 µL) to the test strip before the glucose measurement is complete. Venous whole blood samples at 3 glucose concentrations (50-65, 100-120 and 200-250 mg/dL) were tested using 3 lots of test strips, in replicates of 10 per lot. Values obtained were compared to the comparator method (YSI 2300 STAT Plus). The results of the study demonstrate that that the Assure Titanium Blood Glucose Monitoring System is robust to intermittent sampling.

iv. Testing with Used Test Strips:

A study was performed to assess how Assure Titanium Blood Glucose Monitoring System performs when a used test strip is inserted in a meter.

Fingerstick blood samples from 10 donors and one level of control solution (L1) were tested, using 3 lots of test strips and 3 meters. The test strip was inserted into the meter, a sample was applied to the test strip and the measurement results were recorded. The strip was removed after measurement using the ejection lever and inserted again into the meter within 30 min. This step was repeated three times (three re-insertions), for each test strip. In all cases the Assure Titanium Blood Glucose Monitoring System displayed an error result (E1), demonstrating that insertion of a used test strip into the blood glucose meter does not provide glucose measurement results to the user.

v. Messages for Samples Outside the Measuring Range:

A study was conducted using whole blood samples to demonstrate that the Assure Titanium Blood Glucose Monitoring System provides the appropriate error codes when measured glucose concentrations are outside of the meter's claimed measuring range. If the concentration of a sample is less than 10 mg/dL glucose, the result is flagged by the meter as "Lo". If a sample exceeds 600 mg/dL glucose, the result is flagged by the meter as "Hi". The "Lo" and "Hi" functions were validated and demonstrated to function as intended.

vi. Robustness Study:

Disinfection efficacy studies were performed on the exterior meter materials by an outside commercial testing laboratory, demonstrating complete inactivation of Hepatitis B Virus (HBV) with the chosen disinfectant, Super Sani-Cloth Germicidal Disposable Wipe (EPA Registration Number 9480-4). Robustness studies were also performed by the sponsor demonstrating that there was no change in performance or external materials of the meter after 10,950 cycles of cleaning and disinfection using the chosen disinfectant. The robustness studies were designed to simulate cleaning and disinfection over the 3-year multi-patient use life. The validated cleaning and disinfection instructions are included in the labeling.

d. Hardware, Software and Electronics Integrity

i. Electrical Safety

The Assure Titanium meter is powered by 2 x 1.5V alkaline AAA batteries and does not present an electrical safety hazard. However, the following testing was performed to validate that the Assure Titanium Blood Glucose Meter is insensitive to performance variation under the following electrical stress conditions:

(i) Reverse battery insertion:

A study was performed to demonstrate that the reverse insertion of the battery during the course of normal operations of the Assure Titanium Blood

Glucose Monitoring System does not cause explosions or a fire risk. The direction of the plus and minus ends for each battery were arranged opposite to the indicated directions and the batteries were inserted into the battery box. Functional verification demonstrated that no defects were observed. Also, no explosions or fire risks were observed (no generation of heat as a result of an electrical short).

(ii) Current consumption:

A study was performed to confirm that the current consumption is as described in the design specifications for the Assure Titanium meter. The meter was supplied with 3.0 volts and current consumption for each operation mode (sleep, application waiting, measurement and result display) were measured. The current consumption for all meters for each condition satisfied the evaluation criteria.

(iii) Environment resistance:

A study was performed to confirm that there are no problems with the functionality of the Assure Titanium meter following both high-temperature storage testing (64.9 °C and 95% RH) and low-temperature storage testing (-20.2 °C, humidity N/A). All of the verification results were within the criteria limits and no deterioration in functionality was observed.

(iv) Transport testing:

A study was performed to confirm the drop, vibration, and compression resistance of the Assure Titanium meter. All the results passed the acceptance criteria. Additionally, no risks from sharp cracks or raised points, etc. that could harm the human body were observed.

(v) Mechanical hazards:

A study was performed to confirm that the Assure Titanium meter provides protection against mechanical hazards. After physical checking, no dangerous locations such sharp protrusions capable of injuring the user were found. In addition, in confirming the dangers of movable parts, fingers were inserted between the ejection lever and the device, the battery cover was opened and closed, and the batteries were changed. However, in all of these situations no injuries from pinching were observed.

(vi) Physical trauma to the meter:

A study was performed to confirm that there are no problems with the functionality of the Assure Titanium meter following drop unit testing. The meter was dropped 6 times from a height of 1 m such that each face of the

item made impact with a hardwood board. All of the verification results were within the criteria limits and no deterioration in functionality was observed.

ii. Electromagnetic Interference

The sponsor provided documentation certifying that acceptable electrical safety and electromagnetic compatibility (EMC) testing had been performed and the system was found to be compliant.

L. Demonstrating "Insignificant Risk of an Erroneous Result" –Accuracy

To demonstrate that the Assure Titanium Blood Glucose Monitoring System poses an insignificant risk of erroneous results in the hands of intended users and when performed in CLIA waived-type settings, the sponsor submitted a clinical study which was also used to support FDA clearance under k200788.

1. Comparison Study

a. Study Design

i. Study Sites

Method comparison studies were conducted using capillary fingerstick samples from 396 patients at three clinical sites covering the two intended use settings (one nursing and skilled nursing facility and two endocrinology clinics) across the United States, using untrained intended use operators. Site 1 was a 475-bed nursing and skilled nursing site. The study took place across both the long-term care nursing and rehabilitation unit (also known as a temporary care unit). Sites 2 and 3 were endocrinology clinics.

ii. Operators

In total, 10 operators participated in the clinical study of the Assure Titanium Blood Glucose Monitoring System. The operators selected for the study were representative of operators in a CLIA waived setting and were untrained in the use of the Assure Titanium Blood Glucose Monitoring System (non-laboratory personnel, e.g., registered nurses/licensed practical nurses, medical aides, office manager, receptionist). The operators had no previous experience participating in blood glucose meter studies.

iii. Instructions for Use

The operators were given the meter, test strips, control solutions, the user guide and the quick reference guide in order to self-train. This included self-learning with the system labeling to conduct a control test, view past results, and understand the cleaning/disinfection procedure and recommendations. No other materials or instructions were provided, and the operators received no training on the use of the system.

iv. Subjects (Patients)

In total, 396 subjects were enrolled and participated in the study. Subjects inclusion/exclusion criteria were as follows:

- At least 18 years of age.
- Subjects with or without diabetes from within the intended population.
- Subjects are not undergoing intensive medical treatment in hospital settings such as intensive care units.

The glucose levels tested ranged from 29.0 to 492.5 mg/L, with 32 results falling below 80 mg/dL and 22 results falling above 300 mg/dL. The hematocrit and sodium levels for all subjects tested were recorded. Please see the table below for the number of subjects enrolled at each site.

Site	Site Type	Number of Patients	Glucose Range (mg/dL)	Hematocrit (%)
1	Nursing and skilled nursing facility	130	29.0-405.5	19-44
2	Endocrinology Clinic	165	43.7-492.5	25-51
3	Endocrinology Clinic	101	49.3-367.8	30-54

The clinical study included subjects with reported 390 unique patient medical conditions. Patients received a total of 4066 unique medications, that accounted for 379 drugs classified by generic name, representing 14 main drug classes including nervous system, cardiovascular system, and alimentary tract and metabolism drug classes. Please see the k200788 decision summary for a detailed list of patient medication and medical conditions.

v. Samples

Fresh capillary whole blood from a fingerstick.

vi. Comparative Method (CM)

YSI 2300 Stat Plus (k913806).

b. Results and Analysis

i. Data Analysis

The results from the capillary fingerstick samples obtained from the Assure Titanium Blood Glucose Meter compared to the results from the comparator method (YSI 2300 STAT Plus), per site type, as well as all sites combined are summarized below:

Results for Glucose Concentrations <75 mg/dL:

Site	Within ±5 mg/dL	Within ±10 mg/dL	Within ±12 mg/dL	Within ±15 mg/dL
1	1/1 (100%)	1/1 (100%)	1/1 (100%)	1/1 (100%)
2 and 3	17/26 (65.4%)	25/26 (96.2%)	26/26 (100%)	26/26 (100%)
All sites combined	18/27 (66.7%)	26/27 (96.3%)	27/27 (100%)	27/27 (100%)

Results for Glucose Concentrations ≥75 mg/dL:

Site	Within ± 5%	Within ± 10%	Within ± 12%	Within ± 15%	Within ± 20%
1	80/129 (62.0 %)	122/129 (94.6%)	125/129 (96.9%)	128/129 (99.2%)	129/129 (100%)
2 and 3	163/240 (67.9%)	224/240 (93.3%)	230/240 (95.8%)	235/240 (97.9%)	240/240 (100%)
All sites combined	243/369 (65.9%)	346/369 (93.8%)	355/369 (96.2%)	363/369 (98.4%)	369/369 (100%)

ii. Allowable Total Error (ATE) and Limits for Erroneous Results (LER)

The study performed to support CLIA waiver for Assure Titanium Blood Glucose Monitoring System was analyzed to evaluate whether the clinical data would meet clinically appropriate ATE and LER zones for the sponsor's intended use population. The analysis demonstrates that the percentage of results over the entire measurement range that falls within the ATE zone (within ±12 mg/dL for glucose concentrations < 75 mg/dL or within ±12% for glucose concentrations ≥75 mg/dL) is ≥95%. None of the results were in the LER zone.

2. Operator Questionnaire

Upon completion of the clinical studies, each of the 10 operators completed a questionnaire to evaluate the ease of understanding of the test procedure. The participants found Assure Titanium Blood Glucose Monitoring System easy to use and the instructions in the user manual and QRG clear and easy to follow.

M. Labeling for Waived Devices

The labeling consists of:

1. User Manual
2. Quick Reference Guide
3. Test Strips Package Insert
4. Meter Carton
5. Test Strips Carton

The labeling is sufficient and satisfies the requirements of 21 CFR Part 809.10.

- The Quick Reference Guide and User Manual are written at no higher than a 7th grade reading level.
- The User's Manual and Quick Reference Guide identify the test as CLIA waived.
- The User Manual and Test Strip Package Insert contain a statement that a Certificate of Waiver is required to perform the test in a waived setting.
- The User Manual and Quick Reference Guide contain a statement that laboratories with a Certificate of Waiver must follow the manufacturer's instructions for performing the test. 42 CFR 493.15(e)(1).
- The User Manual, Test Strip Package Insert and Quick Reference Guide provide instructions for conducting quality control procedures.

N. Conclusion:

The submitted information in this CLIA waiver application supports a CLIA waiver approval decision.