CLIA Waiver Determination Decision Summary

A. **Document Number:**

k053110/A001 – A005

B. Purpose for Submission:

Request for CLIA Waiver

C. Measurand (Analyte):

Potassium

D. Type of Test:

Quantitative, potentiometric

E. Applicant:

Abbott Point of Care

F. Test System Name:

i-STAT CHEM8+ System

G. Special Instrument Requirements:

i-STAT1 Analyzer

H. Test System Description:

The i-STAT CHEM8+ System is comprised of the first is the i-STAT1 analyzer is used to run the test cartridge and the i-STAT CHEM8+ cartridge. The CHEM8+ cartridge contains a panel of nine reported tests (sodium, potassium, chloride, carbon dioxide, urea nitrogen, creatinine, glucose, ionized calcium and hematocrit) and two calculated test (anion gap and hemoglobin). The cartridge is a single-use device and is factory calibrated. Once the cartridge is inserted into the analyzer the analysis cycle is automatic and controlled by the software in the analyzer.

I. Demonstrating "Simple":

Test system is: (if NO or N/A provide explanation)

1. Fully automated _X__
   Unitized _X___
   Self contained ____

2. Uses direct unprocessed specimens
_X__Yes ___No

3. Sample type
Fingerstick ____
Venous whole blood _X___
Urine ____
Oral Fluid ____
Nasal Swabs ____
Throat Swabs _____
Other ____

4. Requires only basic, non-technique-dependent specimen manipulation
__X_Yes ___No

5. Requires only basic, non-technique-dependent reagent manipulation
_X__Yes ___No ___N/A

6. Has no operator intervention during the analysis
__X_Yes ___No

7. Requires no technical or specialized training with respect to troubleshooting (interpreting error codes does not constitute troubleshooting)
_X__Yes ___No

8. Requires no electronic or mechanical maintenance
__X_Yes ___No

9. Provides direct readout of results, i.e. requires no calculation or conversions
__X_Yes ___No

J. Demonstrating "Insignificant Risk of an Erroneous Result- Failure Alerts and Fail-safe Mechanisms:

A. Risk Assessment

A report describing the risk assessment is present and the following were tested; incorrect patient results, environmental factors, improper sample handling and integrity, cartridge handling, analyzer handling and interfering substances. The instrument performs a self check each time a test is performed to detected any mechanical or electronic problems, proper fluid movement, insufficient sample to run the test, temperature. The affects of hemolysis, lipemia and icterus on the results. See the mitigations for the risks below.

B. Fail-safe and Failure Alert Mechanisms.

1. General Recommendations.

    a. Lockout features - The electronic simulator (internal or external) must be run every 24 hours or a test can not be performed.

    b. Monitors of environmental conditions – a series of automated on-line quality measurements that monitor environmental, sensors fluids and instrument each time a test is performed.

    c. Internal procedure controls – Quality Checks that monitors the sensitivity and accuracy of the detection channels every 24 hours when the analyzer is in use.

    d. Electronic Controls -The electronic simulator (internal and/or external) checks that the analyzer is reading signals from the cartridge correctly.

    e. Calibration – factory set, a calibrant solution is included in and run with each cartridge to rehydrate the sensors. Electrical signals are produced and compared to expected levels to verify the sensors are working properly.

    f. Specimen Identification - sample ID can be entered manually or by barcode scanner into the system.

2. External Control Materials.

    a. External Control material recommended - Liquid control material to check the chemistry analytes and hematocrit.
    b. Frequency recommendation – each new shipment, each new lot and monthly to check storage.
    c. Directions for use – step by step procedure is included on the quick reference guide.
    d. Storage and stability – follow the manufacturers instructions
    e. Number of levels – Two levels chemistry and 2 levels for Hematocrit.
    f. Manufacturer - i-STAT and RNA Medical Hematocrit

3. Validation/Verification Studies for Fail-safe and Failure Alert Mechanisms.

    a. Stress studies – list the types of testing that was performed.
    Reagent integrity (cartridge storage), sample handling, temperature (instrument), software, electronics.
    b. Contains fail-safe mechanisms that render no result when the test system malfunctions and rendering no test result when results are outside the reportable range.
    The system will display an error code if the system malfunctions or there is a sample problem. If the value is above or below the

reportable range the instrument will display < lowest reportable range value or > with highest reportable range value.

The risk of harm to patients from the analysis of a hemolyzed is mitigated by the unlikely probability of occurrence. Data from a large reference laboratory that receives samples from doctors' offices and nursing homes (intended sites of use for the CLIA waived tests) and literature shows that significant hemolysis is present in only 0.13% of samples. Also the number of patients presenting in doctor's offices and nursing homes with critically low potassium would be small. The third National Health and Nutrition Examination Survey (NHANES III) examined potassium levels for 18,723 non-institutionalized people (representative of the population that would be tested at these sites with the waived product). The ranged of observed values was 2.51-6.94 mmol/L. There were no observed values below the critical value of 2.5 mmol/L.

References:

Data from Laboratory Corporation of America
Errors in Laboratory Medicine, Bonini et al.,Clinical Chemistry 48:5 691-698 (2002) This assumes 10 tests ordered per sample.
Sex and Age Differences in Serum Potassium in the United States, Wysowski, Kornegay et al., Clinical Chemistry 2003; 49:190-2

K. Demonstrating "Insignificant Risk of an Erroneous Results" (Accuracy)

A. Testing Sites, Participants and Testing Duration.

The testing was performed at five different sites; Two nursing homes and three Physicians offices. There were 13 operators were nurses, nursing assistants, unit managers and medical assistants and testing lasted four weeks.

B. Quantative Tests:

1. Comparative Method (CM), Type.

The Comparator Method is a Type B traceable method. Samples were assayed four times and the average was used in the statistical analyses. Traceability of the method was provided.

2. Descriptive Statistical Analysis.

Ordinary linear least square and weighted linear least square regression analysis were used. The weights used are inversely proportional to the estimated variance of the WM values at discrete intervals along the scale of CM values.

a. Regression analysis for all sites

Test	N	Intercept (β_0)	95% CI (β_0)	Slope (β)	95% CI (β)
Potassium (OLS)	402	0.026	(-0.007, 0.06)	0.994	(0.987, 1.002)

Bias Table:

Test	Medical Decision Point(s)	
Potassium	3 mmol/L – 0.008 (0.26%)	5.8 mmol/L – 0.09 (0.15%)

3. Performance Criteria of the working Waiver Method (WM)

   a. Allowable Total Error (ATE)

   CLIA limits for proficiency testing were selected for the ATE limits. The lower 95% exact confidence bound should exceed 92% and 95% of WM values must be with the ATE limits. The ATE limits for each analyte and results can be found in the tables below:

ATE Acceptance Criteria

Test	**Limit, ±**
Potassium	0.5 mmol/L

Percentage of observations that fall within the ATE zone for the low, middle, and high ranges of the CM.

Range of CM values (mmol/L)	Total number of samples	Number of samples within of ATE	Percent of samples within of ATE
2.0 to 3.49	28	28	100%
3.5 to 4.99	344	344	100%
5.0 to 9.0	30	30	100%
2.0 to 9.0	402	402	100%

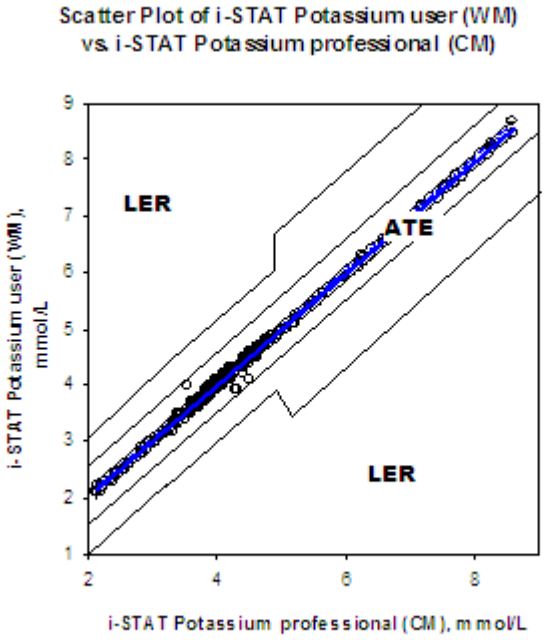
Percentage of observations over the entire measuring range that fall within the ATE zone with 95% exact lower confidence bound.

Test	**Nt**	**Ntw**	**% within**	**95% lower CB**
K	402	402	100	99.26

The percentage of the samples over the entire range that fall within the ATE zone was 100% (402/402) with a lower bound of 95% confidence interval of 99.3%.

b. Zones of Limits for Erroneous Results (LER)

The LER zone, are limits for the differences between the WM and the CM. Results inside these limits posing a risk to patient safety. None of the data points fell within the LER zones.



C. Qualitaive Tests:

1. Comparative Method (CM), Type.
   Not applicable
2. Statistical Analysis.
   a. Device performance with analyte concentration near the cutoff.
      Not applicable
   b. Test performance with analyte concentration overall.
      Not applicable

M. Proposed Labeling:

1. The labeling is sufficient and it satisfies the requirements of 21 CFR Part 809.10 and the test procedures steps are at no higher than a 7th grade reading level and provides pictures and diagrams.
2. The Quick Reference Instructions are easy to read and is written at a 7th grade reading level.
3. Instrument Manual is easy to read and contains the required instruction information.

N. Type of Education Material Provided:

An Instructional CD is also available.

O. <u>Conclusion:</u>

The Submitted Information in this CLIA Waiver is complete and Supports a Waiver decision.

P. Other Supportive Test System Information:

Q. Administrative Information:

1. Applicant contact information:

   a. Name of applicant:

   i-STAT Corporation

   b. Mailing address:

   104 Windsor Center Drive
   East Windsor, NJ 08520

   c. Phone #:

   609-469-0242

   d. Fax #:

   609-443-9310

   e. E-mail address (optional):

   paul.vanderwerf@abbott.com

   f. Contact:

   Paul VanDerWerf, Ph.D.

2. Review documentation:
   The Potassium analyte for the WM is not statistically significantly different from those of the CM.

3. Waiver Performance for Labeling:

   The following labeling information is what we recommended to the sponsor.

   Results of CLIA Waiver Study

Potassium (K)

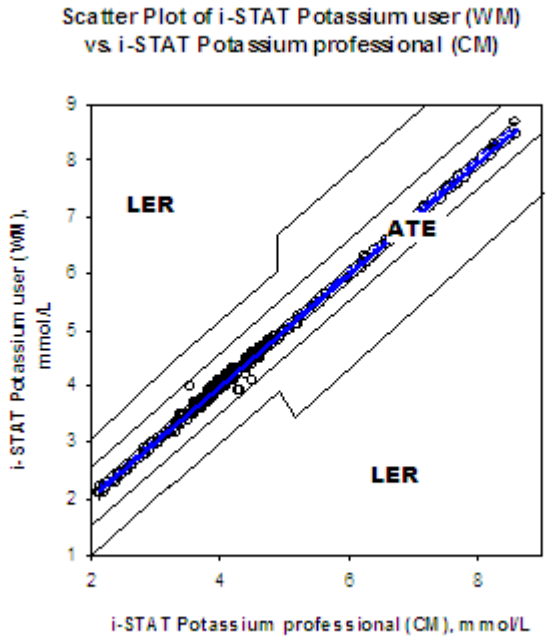
A clinical study was conducted at five sites located in two regions of the United States. Two nursing homes in Florida and three Physicians Offices in Illinois. There were a total of 13 operators distributed as follows; three sites had three operators and two sites had two operators. Among thirteen participants, six were non-healthcare professionals and seven were healthcare professionals who were not given any training on the use of the test operated the I-stat device using the Chem 8+ cartridges (WM) at the five sites. The study involved running 408 samples (362 patient samples and 40 spiked samples) over a one month period at 5 sites. Three patient samples and three spiked samples were repeated due to error.
The comparative method was the i-Stat system run by five laboratory professionals (one per site). To reduce measurement variability, the measurement of samples was repeated four times and average value was used (referred as CM). Specimens were collected by venous method. A Lithium Heparin green top tube was used to draw 4 mL of sample to be used on both the waiver method and the comparator.

The study was intended to demonstrate that after reading only the test instructions, participants were able to get results on the I –Stat Chem8+ cartridge that were as accurate as those obtained on comparator using the following performance limits: Allowable Total Error (ATE) encompasses values of i-Stat result (averaged from four measurements done by laboratory professionals) ± 0.5 mmol/L. The results of the study were following:

Range of CM values (mmol/L)	Total number of samples	Number of samples within of ATE	Percent of samples within of ATE
2.0 to 3.49	28	28	100%
3.5 to 4.99	344	344	100%
5.0 to 9.0	30	30	100%
2.0 to 9.0	402	402	100%

The percentage of the samples over the entire range that fall within the ATE zone was 100% (402/402) with a lower bound of 95% confidence interval of 99.1%. In addition to the ATE zone, it was considered a zone where if a sample fall in this zone then there has been a failure to properly identify blood potassium concentrations (zone of the Limits for Erroneous Results (LER) see graph below). In the study, no samples were in the LER zone (0% with an upper bound of 95% confidence interval of 0.9%).

The scatter plot of the study results with ATE and LER zones is presented by the figure below:



The descriptive statistics of the differences between WM and CM results are presented by the table below:

Range of CM values (mmol/L)	Average difference	2.5th percentile of differences	97.5th percentile of differences
2.0 to 3.49	0.0003	-0.1	0.1
3.5 to 4.99	0.0028	-0.1	0.1
5.0 to 9.0	-0.0225	-0.1	0.087

The WM and CM results were compared by ordinary least squares regression analysis: a slope was 0.994 with 95% CI: 0.987 to 1.0; and an intercept was 0.025 with 95% CI: -0.007 to 0.057. The systematic differences between WM and CM results estimated by regression analysis are presented in the table below:

CM (mmol/L)	Systematic difference between WM and CM (mmol/L)
3	0.0076
6	-0.0098