TaiDoc
泰博科技股份有限公司
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Letter of Declaration

Jun 11, 2012

Herewith we would like to confirm for the following product:

Product Name:
GlucoCheck XL

Manufactured by:
TaiDoc Technology Corp.
6F, No.127, Wugong 2nd Rd., Wugu District, New Taipei City 24888, Taiwan.

And suppliy to:
Aktivmed GmbH
Prinzregentenplatz 1
D-86150 Augsburg

TaiDoc Technology Corp. would like to declare that GlucoCheck XL is identically constructed with the blood glucose monitoring system, model TD-4277.

GlucoCheck XL is produced under the same technology and specification as TD-4277.

Any changes in the specification and/or technology in respect to these products TaiDoc will inform immediately and without any delay to Aktivmed GmbH.

On behalf of

Kenny Chi, VP of Sales
TaiDoc Technology Corp.

KENNY_CHI(紀鴻志)

Final Report

Evaluating system accuracy of blood glucose monitoring systems for self-testing in managing diabetes mellitus [following EN ISO 15197:2003 - *7.3 System accuracy evaluation*]

URIGHT TD-4277

*Project code **IDT-1239-AA***

Date: 16JUL2013

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Application Number: MP-2012-009
Application: 13.10.2012
Positive decision: 13.11.2012

Amendment application: 15.03.2013
Amendment positive decision: 09.04.2013

Health Authority (MPG)

BfArM Bundesinstitut für Arzneimittel und Medizinprodukte
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Application Number: 95.06 – 5661 - 7848
Application: 13.10.2012
Positive decision: 24.10.2012

Amendment application: 23.03.2013
Amendment positive decision: 04.04.2013

Subject Insurance

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1 Introduction

Main objective of modern diabetes therapy is to achieve near normal blood glucose levels in order to prevent late damages. Self monitoring devices allow for metabolic control by patients and doctors and for a flexible therapy adjustment by the patient himself. As insulin therapy is controlled by the measured values high-quality blood glucose monitoring systems (BGMS) are required.

EN ISO 15197:2003 [1] is an international standard specifying requirements for in vitro glucose monitoring systems for self-testing in managing diabetes mellitus.

The minimum acceptable accuracy for results produced by a glucose monitoring system shall be as follows: Ninety-five percent (95%) of the individual glucose results shall fall within ± 0.83 mmol/l (15 mg/dl) of the results of the manufacturer`s measurement procedure at glucose concentrations < 4.2 mmol/l (< 75 mg/dl) and within ± 20% at glucose concentrations ≥ 4.2 mmol/l (≥ 75 mg/dl).

In this study system accuracy evaluation according to EN ISO 15197:2003 was performed for the investigated system URIGHT TD-4277.

2 Material and Methods

2.1 Study objective

The aim of this study was to collect measurement data from capillary blood with defined distribution of glucose concentrations in order to perform system accuracy evaluation according to EN ISO 15197:2003 for URIGHT TD-4277. The comparison measurements were performed on YSI 2300 STAT PLUS. Measurements on Cobas c111 were used for an additional evaluation.

2.2 Inclusion criteria

- Male or female subjects with diabetes type 1 or 2 or subjects without diabetes
- For provoked blood glucose excursions: male or female subjects with diabetes type 1 or 2 and intensified conventional insulin therapy or insulin pump
- Written informed consent
- Minimum age of 18 years
- With legal capacity and able to understand nature, meaning and consequences of the clinical trial

2.3 Exclusion criteria (shortened list)

- Pregnancy or lactation period
- Severe acute disease or chronic disease with potential risk during the trial
- Current constitution of the subject which does not allow to take part in the study
- Legal incompetence or accommodated in an institution
- Language barriers precluding adequate compliance with the study procedures
- Dependency from the sponsor or the clinical investigator

2.4 Study duration per subject

- Up to 3 hours

2.5 Screening

- Information about the study (aims, procedures, risks, duration)
- Written informed consent
- Anamnesis, physical examination and urine pregnancy test (if applicable)

2.6 Study devices

2.6.1 URIGHT TD-4277

Manufacturer: TaiDoc Technology Corporation
3F, 5F., No. 127, Wugong 2nd Road, 24888 Wugu Dist.
New Taipei City, Taiwan

- *Technical specifications*

Blood sample:	Fresh capillary and venous whole blood
Sample volume:	0.5 µl
Measuring range:	20 - 600 mg/dl (1.1 - 33.3 mmol/l)
Analysis time:	5 sec
Operating temperature:	10 - 40°C
Operating humidity:	< 85%
Hematocrit range:	20 - 60%
Measurement technology:	Glucose dehydrogenase
Calibration:	Plasma equivalent
Coding:	No coding

- *Meters, test strips, control solutions*

URIGHT TD-4277	
Serial number	*Study code*
4277112040000163	*A1*
4277112040000185	*A2*
427711204000021F	*A3 (backup)*
427711204000020E	*not used*
4277112040000196	*not used*
4277112040000174	*not used*

TD-4277 Test Strips		
Lot	Lot number	Expiry
1	TD12L112-BOG	2014/06
2	TD13A128-BOG	2014/08
3	TD13C113-BOG	2014/09

Control solution	Lot number	Expiry	Target range [mg/dl]
TaiDoc Control Solution	WA12K002	2014/11	Lot 1: 121 - 163 Lot 2: 118 - 160 Lot 3: 120 - 162
TaiDoc Control Solution	B12D001	2014/04	Lot 1: 281 - 380 Lot 2: 277 - 375 Lot 3: 279 - 377

2.6.2 YSI 2300 STAT PLUS

- Manufacturer: YSI Incorporated, Yellow Springs, Ohio, USA
- Method / chemistry: Glucose oxidase (GOD-H_2O_2)
- Sample: capillary plasma
- Certificate of interlaboratory comparison is available
- Double test = measurement with 2 electrodes

Trueness and precision

- Trueness was assessed according to CLSI EP15-A2 [3]
  by assaying Bioanalytical Standards (Glucose), YSI Incorporated, Yellow Springs, OH, USA
- Precision was assessed according to CLSI EP15-A2 [3]
  by assaying AutoCheck 5+, Radiometer Medical ApS, Brønshøj, Denmark
- Autocheck 5+ control samples were measured on each study day to confirm constant trueness and precision according to the RiliBÄK guideline [4].
- In addition Bioanalytical Standards (Glucose) were measured on each study day to confirm constant trueness and precision.

2.6.3 Cobas c111

- Manufacturer: Roche Instrument Center, Rotkreuz, CH
- Method / chemistry: Hexokinase
- Sample: capillary plasma
- Certificate of interlaboratory comparison is available

Trueness and precision

- Trueness was assessed according to CLSI EP15-A2 [3] by assaying Standard Reference Material (SRM) 965b, National Institute for Standards and Technology (NIST), Gaithersburg MD, USA
- Precision was assessed according to CLSI EP15-A2 [3] by assaying Precipath U / Precinorm U, Roche Diagnostics GmbH, Mannheim, Germany
- Precipath U / Precinorm U control samples were measured on each study day to confirm constant trueness and precision according to the RiliBÄK guideline [4].
- In addition NIST SRM 965b samples were measured on each study day to confirm constant trueness and precision.

2.6.4 OPTI CCA-TS

- Manufacturer: OPTI Medical Systems, Inc., Roswell, GA, USA
- Method / chemistry: Optical fluorescence (for oxygen partial pressure)
- Sample: capillary whole blood
- Certificate of interlaboratory comparison is available

Trueness and precision

- Opti™ Check (OPTI Medical Systems, Inc., Roswell, GA, USA) control samples were measured on study days prior to usage to confirm constant trueness and precision according to the RiliBÄK guideline [4].

2.6.5 Maintenance, adjustment, control procedures

- For all study devices maintenance, adjustment and control procedures were followed in accordance with the manufacturers' instructions.

2.7 Control measurements with blood glucose monitoring systems

- Control solutions / levels see 2.6 Study devices.
- Measurements were performed according to manufacturer's instructions
- Unsuccessful control measurements had to be repeated once.
- If the result was still not within the range, the meter had to be cleaned following the system specific cleaning instructions. If the result was still not within the range, the meter had to be changed and the procedure reiterated.
- Available levels of control solutions were measured daily before measurement of blood samples. In addition control measurements were performed with test strips from each test strip vial using one level of control solution.
- A system passed the qualification when all measurements were inside the target ranges given by the manufacturer.

2.8 Determination of hematocrit

- Centrifugation of capillary whole blood in heparinised capillaries
- Reading of hematocrit level on alignment chart
- Double test (if both measurements were successful the mean value was calculated)
- Determination before or after measurements with BGMS
- Certificate of interlaboratory comparison is available

Trueness and precision

- Liquichek™ Hematology-16 Control (Bio-Rad Laboratories, Irvine, CA, USA) control samples were measured on study days prior to usage to confirm constant accuracy and precision according to the RiliBÄK guideline [4].

2.9 Experiment

2.9.1 Requirements according to ISO 15197

2.9.1.1 Samples

- ≥ 100 fresh capillary blood samples collected by skin puncture were prepared, processed and applied according to the manufacturer's instructions
- Only unaltered capillary blood samples were used for glucose concentrations of ≥ 50 - < 400 mg/dl
- For samples of < 50 mg/dl and ≥ 400 mg/dl glucose concentration could be adjusted
- Exclusion criteria for samples were defined based on the manufacturer's instructions for use (see also additional exclusion criteria for samples)
- Aliquots were removed from each sample immediately before the first and immediately after the last measurement with the blood glucose monitoring system for duplicate measurement with the comparison method.
- Defined distribution of glucose concentrations was obtained:

Percentage of samples [%]	Glucose concentration [mg/dl]
5	< 50
15	≥ 50 - < 80
20	≥ 80 - < 120
30	≥ 120 - < 200.5
15	≥ 200.5 - < 300.5
10	≥ 300.5 - < 400
5	≥ 400

Samples were assigned to the respective category according to the glucose concentration measured with YSI 2300 STAT PLUS or Cobas c111, respectively.

- Once a concentration category was filled, no more samples were added to that category

2.9.1.2 Reagent system

- Three lots of reagent system units were examined.
- At least 200 reagent system units from at least 10 packages were used
- Reagent system units were taken from the same package for each sample
- Packages were changed approximately every 10 subjects

2.9.1.3 BG monitoring systems

- Users have received proper training
- Devices were properly maintained
- Required adjustment and control procedures were followed in accordance with the manufacturer's instructions.
- Samples were measured with 2 different devices

2.9.1.4 Environment

- Measurements using the blood glucose monitoring system were performed at 23 °C ± 5 °C

2.9.1.5 Evaluation procedure

- Results from comparison methods were evaluated to verify sample stability
  (If change between first and last result > 4% at glucose > 100 mg/dl or > 4 mg/dl at glucose ≤ 100 mg/dl, results for that sample had to be rejected)

2.9.2 Additional exclusion criteria for samples

- Humidity had to be between < 85%
  (based on manufacturer's instructions for use)
- Glucose concentration measured with the comparison methods had to be within the measurement range of 20 - 600 mg/dl
  (based on manufacturer's instructions for use)
- Hematocrit had to be between 20 and 60%
  (based on manufacturer's instructions for use)
- Exclusion of samples possibly containing endogenous and exogenous interferents: subjects' anamnesis and medication was reviewed by a physician in comparison to the interferents given in the manufacturers' instructions for use or as specified by the customer
- Acceptance criterion for double measurements (comparison methods):
  If values of a double measurement had a coefficient of variation (CV) ≥ 5%, then the results for that sample had to be rejected.

2.9.3 Determination of glucose concentration - sample preparation

- Native samples: capillary whole blood from finger prick
  - for measurements with BG meters: sample taken directly from finger prick
- Samples designated to be adjusted to < 50 mg/dL or ≥ 400 mg/dL:
  - capillary whole blood collected in lithium-heparin Multivettes (Sarstedt AG & Co., Nümbrecht, D).
  - Adjustment was performed according to EN ISO 15197:2003 by either
    - incubation
    - supplementation with glucose (stock solution: 40% in 0.9% NaCl)
- For measurements with comparison methods: capillary plasma
  - obtained from capillary whole blood from finger prick collected in lithium heparin Monovettes, Multivettes (Sarstedt AG & Co., Nümbrecht, D)

2.9.4 Determination of glucose concentration - measurement procedure

- Screening measurement with Accu-Chek® Aviva Nano, Roche Diagnostics (optional)
- Determination of hematocrit (before or after measurements with test systems)
- Taking of 1st sample for comparison methods
- Measurement with devices:
  URIGHT TD-4277 – A1 Lot 1: TD12L112-BOG
  URIGHT TD-4277 – A2 Lot 1: TD12L112-BOG
- Taking of 2nd sample for comparison methods (native samples only)
- Measurement with devices:
  URIGHT TD-4277 – A1 Lot 2: TD13A128-BOG
  URIGHT TD-4277 – A2 Lot 2: TD13A128-BOG
- Taking of 3rd sample for comparison methods (native samples only)
- Measurement with devices:
  URIGHT TD-4277 – A1 Lot 3: TD13C113-BOG
  URIGHT TD-4277 – A2 Lot 3: TD13C113-BOG
- Taking of 4th sample for comparison methods
- Plasma separation and comparison measurements
- Determination of oxygen partial pressure (OPTI CCA-TS) to exclude elevated levels >100 mmHg (adjusted samples only)

2.10 Data analyses

2.10.1 Analysis of system accuracy according to EN ISO 15197:2003 [1]

- performed vs. YSI 2300 STAT PLUS, Cobas c111
- including:
  - Bias analysis according to Bland and Altman [5]

    Analysis done with Analyse-it for Microsoft Excel (version 2.30) [6]
  - Regression analysis according to Passing and Bablok [7]

    Analysis done with Analyse-it for Microsoft Excel (version 2.30) [6]

2.10.2 Consensus Error Grid analysis according to Parkes [2]

- performed vs. YSI 2300 STAT PLUS, Cobas c111

3 Results

3.1 Time span of experiments

- 29.04.2013 – 16.05.2013

3.2 Study subjects

- Total number of subjects screened: 108
- Total number of subjects completed: 108
  100 → analysis according to ISO 15197

3.3 Equipment failures

- No equipment failures

3.4 Adverse Events

- No adverse events

3.5 Samples

	Lot 1	Lot 2	Lot 3
Samples taken from 108 different subjects	120	119	117
Samples rejected because of			
- comparison method control measurement not in range	1	1	1
- missed stability criterion	7	2	1
- concentration category different between lots and/or comparison methods	6	7	7
- concentration category was already filled	6	6	6
- incomplete measurement series	0	1	1
- subject already provided valid measurement	0	2	1
Minimum and maximum of glucose concentrations (samples included in evaluation)			
- minimum [mg/dl]	37.475	37.475	37.475
- maximum [mg/dl]	487.5	487.5	487.5
Environmental conditions during measurements (samples included in evaluation)			
- temperature [°C] *target range: 23 ± 5 °C*	20.3 – 23.9	20.3 – 24.0	20.3 – 24.0
- humidity [%] *target range: <85%*	32.0 – 56.5	32.0 – 56.5	32.0 – 56.5
Hematocrit (samples included in evaluation)			
- hematocrit [%] *target range: 20 – 60%*	35.0 – 55.0	35.0 – 55.0	35.0 – 55.0

3.6 System accuracy analysis versus YSI 2300 STAT PLUS

3.6.1 Summary of system accuracy analysis following EN ISO 15197:2003

3.6.1.1 Summary of combined system accuracy

n = 200	**Combined system accuracy**	**Criteria of EN ISO 15197:2003 met?**
Lot 1: TD12L112-BOG	198 / 200 (99.0%)	YES
Lot 2: TD13A128-BOG	198 / 200 (99.0%)	YES
Lot 3: TD13C113-BOG	196 / 200 (98.0%)	YES

3.6.1.2 Summary of bias analysis

n = 200	**Bias [mg/dl]**	**95% Limits of agreement [mg/dl]**	**Bias [%]**	**95% Limits of agreement [%]**
Lot 1: TD12L112-BOG	-9.458	-39.551 – 20.636	-5.2	-18.7 – 8.2
Lot 2: TD13A128-BOG	-6.484	-35.963 – 22.996	-3.6	-17.9 – 10.7
Lot 3: TD13C113-BOG	-6.687	-37.295 – 23.921	-3.9	-18.4 – 10.7

3.6.1.3 Summary of regression analysis

n = 200	**Regression**
Lot 1: TD12L112-BOG	y = 0.94 x + 0.50
Lot 2: TD13A128-BOG	y = 0.97 x – 0.20
Lot 3: TD13C113-BOG	y = 0.96 x – 0.60

3.6.2 Summary of Consensus Error Grid analysis

	n	Percentage of results within zones A and B
Lot 1: TD12L112-BOG	200	100%
Lot 2: TD13A128-BOG	200	100%
Lot 3: TD13C113-BOG	200	100%

- See appendix

3.7 System accuracy analysis versus Cobas c111

- See appendix

4 Summary and Conclusions

- Accuracy evaluation following to EN ISO 15197:2003 and Consensus Error Grid analysis were performed for URIGHT TD-4277 with three different lots of test strips.
- Comparison method: YSI 2300 STAT PLUS

Accuracy evaluation following EN ISO 15197:2003

- Minimum acceptable accuracy according to EN ISO 15197: 2003:
  ≥ 95% of the individual results shall fall within ± 15 mg/dl of the reference measurement at glucose concentrations < 75 mg/dl and within ± 20% at glucose concentrations ≥ 75 mg/dl.
- In the current evaluation
  - 99.0% of results with URIGHT TD-4277 Lot 1
  - 99.0% of results with URIGHT TD-4277 Lot 2
  - 98.0% of results with URIGHT TD-4277 Lot 3

  fell within the limits for system accuracy defined by EN ISO 15197:2003, thus fulfilling the standard's system accuracy criteria with each test strip lot.

Consensus Error Grid analysis

- In the current evaluation, 100% of results fell within zones A and B of the Consensus Error Grid for all systems.

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Appendix