Institute of Diabetes "Gerhardt Katsch" Karlsburg
(IDK)

Report

Evaluation of system accuracy of the blood glucose monitoring system "Tyson Bio HT-100" according to DIN EN ISO 15197: 2015

Sponsor:	Tyson Bioresearch, Inc. 5F, No.16, 18, 20, 22, Kendong 3rd RD., Zhunan Township, Miaoli County 35053, Taiwan
The study was conducted in:	Institute of Diabetes GmbH. Greifswalder Straße 11 e 17495 Karlsburg
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1. Introduction

The aim of the modern diabetes therapy is the maintenance of near normal blood glucose concentrations to prevent both hypo- and hyperglycaemic excursions that have been closely associated with the development of acute and late complications of the disease.
Blood glucose monitoring/measurement systems, which can be used for self-determination of the blood glucose by the patient, are helpful for a better metabolic control by the patients themselves and by the physician and allow a more flexible adjustment of the individual medication/therapy.
To achieve this goal, any insulin dose adjustment should precede the blood glucose self control using blood glucose monitoring systems with a high quality and measurement accuracy.
The directive DIN EN ISO 15197 [1] demands strict international quality standards for the system accuracy of blood glucose monitoring systems (BGMS). The DIN EN ISO 15197:2015 [2] represents a revision of the DIN EN ISO 15197:2003 [1]. The minimal acceptable accuracy for measurements using BGMS is defined as follows:
For blood glucose concentrations <5.55 mmol/l (< 100 mg/dl) the glucose values are allowed to differ in comparison to the reference method up to ± 0.83 mmol/l (± 15 mg/dl).
In the case of blood glucose concentrations of ≥5.55 mmol/l (≥ 100 mg/dl) only deviations of less than 15 % as compared to the reference method are acceptable.
In addition, the above criteria must be met by at least 95 % of the measured values.
According to §23b MPG, the present study has tested the system accuracy in accordance to DIN EN ISO 15197:2015 for the system Tyson Bio HT-100.

The glucose monitoring system had a CE certification.
Volunteers were insured by an insurance agency.

2. Aim

The aim of this investigation was to proof the system accuracy of the in accordance with the directive DIN EN ISO 15197: 2015. Reference measurements were performed with the Cobas C111.

3. Study design

Capillary blood, taken from the fingertip of patients (skin disinfection before puncture with a lancet), was used for the measurement of blood glucose concentration by the test- (Tyson Bio HT-100) and reference method (Cobas C111).

3.1 Test persons

The volunteers had to meet the following inclusion criteria:

- Male or female patients with hypo-, normo- or hyperglycaemia
- The written informed consent had to be signed.
- The volunteers must be older than 18 years.
- The volunteers have legal capacity and are able to understand meaning, nature and possible consequences.
- The subjects will receive 10.00 € for expenses.

The exclusion criteria:

- Pregnancy or lactation.
- Acute or chronic diseases with the risk of aggravation by the measure.
- A current constitution which does not allow participating in the study.

3.2. Study period
The blood withdrawal in a patient took 2 to 5 minutes.

3.3. Screening
To attract potential subjects for the study, peoples were first informed about the objective, procedure, risk and duration of the study. After declaration of willingness to participate in the study, written consent from the volunteer was requested. On the experimental day, good physical fitness was a prerequisite for blood sampling.

3.4. Risks of experimental procedure / termination criteria
The blood sampling was executed by qualified persons under strict hygienic conditions, using only disposable material to minimize the risks for the subjects. In case of discomfort of a subject, blood sampling was interrupted.

3.5. Material and methods

3.5.1. Test device Blood Glucose Monitoring System **Tyson Bio HT-100**

Manufacturer: Tyson Bioresarch, Inc.
5F, No.16, 18, 20, 22, Kendong 3rd RD.,
Zhunan Township, Miaoli County 35053, Taiwan

Technical data:

Blood sample:	Venous and Capillary whole blood
Sample volume:	0.7 µl
Glucose measurement range:	20 –600 mg/dl
Measuring time:	5 sec
Working temperature:	10 – 40°C
Relative humidity:	10 – 90 %
Hematocrit:	0 – 70 %

For the tests, two blood glucose monitors Tyson Bio HT-100 were available and used during the tests.

Serial number and study code of the provided two monitors:

Serial number	Study code
M18WA003762	GC1
M18WA003765	GC2

Test strips
In total, 800 test strips from each of 3 lots were available. Reagent systems from 10 packs were used per lot. The following lots were included into the tests:

Test strips		
Numbering	**Lot No.**	**Expiration date**
Lot 1	MSH022G006	2019-11-22
Lot 2	MSH022G008	2019-11-22
Lot 3	MSH022G066	2019-11-22

Control measurements
The control measurements were carried out using three control solutions, whose characteristics are listed in the following table:

Control solution	**Lot No.**	**Expiration date**	**Target area (mg/dl) of test strips** Lot 1, Lot 2 and Lot 3
Level High:	MDH023A004	2019-11-20	179 - 269
Level Normal:	MDH023A001	2019-11-15	69 - 129
Level Low:	MDH023A003	2019-11-20	29 - 59

The measurements were performed according to the instructions by the manufacturer. On each study day before the test measurements, control measurements in each range and for each test strip lot and each monitor were performed (Excel table "controls").
The system was found to be appropriate when the control measurements fell into the range that has been specified by the manufacturer.
The results of the control measurements were within the desired range, so that no device had to be replaced.
The measurements of the control solution Normal had in all three Lots in any case not more than 15 % deviation from the calculated mean. For the control solution High and Low in individual cases measurements with more than 15 % deviation from the calculated mean were registered. (High range: 2 of 18 in Lot1, 1 of 18 in Lot 3, Low range: 1 of 18 in Lot 1,2 and 3)

3.5.2. Reference device

COBAS C111*

Manufacturer:	F. Hoffmann-La Roche AG, Konzern-Hauptsitz Grenzacherstr. 124, CH-4070 Basel, Schwitzerland
Method:	Hexokinase
Probe:	Lithium-Heparin-Plasma sampled and separated from capillary blood
Sample volume:	2 + 75 µl
Glucose measurement range:	1,98 - 720 mg/dl (to 40 mmol/l)
Measuring time:	8 min
Working temperature:	15 - 32°C
Relative humidity:	30 – 80 %
Calibration:	at 198 mg/dl

Accuracy and Precision
The proof of accuracy and precision was performed by use of device specific controls, Cobas Controls PreciControlClinChem Multi 1 and 2 with normal (86 - 116 mg/dl) or high (200 -

272 mg/dl) glucose concentration. The standards were measured on the test day, before, during and after the test series.

Maintenance, adjustment and control procedures
For all the equipment used during the study, the control procedure has been implemented according to the manufacturer's instructions.

3.5.3. Determination of hematocrit

The procedure was performed in accordance with DIN 58933-1. The blood was sampled in heparinized micro-hematocrit capillaries (Laboratory Glassware, Marienfeld, Germany), which were closed and centrifuged thereafter (Hettich centrifuge HAEMATOKRIT 200; Germany). Reading the hematocrit value was performed by using a Nomogram.

4. Execution of the study in accordance with the requirements of DIN EN ISO 15197:2015

4.1. Samples

A total of 100 capillary blood samples were taken. After evaluation of glucose concentration ranges using the reference method Cobas C111, exactly 100 samples were included into the stat.
To reach the lower blood glucose ranges < 80 mg/dl, the glucose concentration was decreased by storage of the samples at 37°C (stored).
To reach the higher blood glucose ranges, the lithium-heparin-blood (300 µl) was spiked with a 40 % glucose solution (B. Braun, Melsungen, Germany) (spiked).
For the measurements of original blood samples (original), 300 µl blood were sampled from the fingertip into Lithium-Heparin tubes (Mikrovetten®, Sarstedt AG & Co., Nümbrecht, Germany). Thereafter, blood was divided into 2 aliquots, which were used for reference measurements (Cobas) before and after test strip measurements. The first reference sample was analysed directly after the sampling procedure and the second one directly after the test strip measurements. In accordance with the requirements as described in DIN EN ISO 15197:2015, samples of the following concentration ranges were included into the procedure:

Range	Glucose (mg/dl)	Percentage of samples according to DIN EN ISO	Sample handling
1	≤50	5	(5 changed)
2	> 50 bis 80	15 (8 unchanged)	(7 changed, 8 unchanged)
3	> 80 bis 120	20 (all unchanged)	(all unchanged)
4	> 120 bis 200	30 (all unchanged)	(all unchanged)
5	> 200 bis 300	15 (all unchanged)	(all unchanged)
6	> 300 bis 400	10 (5 unchanged)	(5 unchanged, 5 changed)
7	> 400	5	(4 changed, 1 unchanged)

The assignment to the concentration ranges based on the results of the reference measurements that have been done using the Cobas C111.

4.2. Blood glucose monitoring systems

Before start of the study, medical technical personnel were instructed in correct handling of the measuring systems. The devices had been properly maintained. Strips of each test lot were measured on two different devices.

4.3. Environmental conditions in the laboratory

During the study, room temperature ranged between 20.5 and 22.1°C and the humidity between 47 and 54 %. (Excel table "conditions during the test"). So the prescribed external conditions were met for the blood glucose measurement systems (see characteristic of the test and reference device).

4.4. Additional exclusion criteria

The glucose concentration ranges were covered in accordance with the ranges in the table (see 4.1.). Criterion for the exclusion should be a difference of more than 4 % between reference value 1 and 2, a failure during the measurement was documented, or the range of measurements was already completed. No data must be excluded.
The haematocrit of the samples should range between 0 - 70 % (a set in the manual of the manufacturer), which was observed in all samples. Accordingly, there was no reason to exclude blood samples due to haematocrit abnormalities. Only those data were included if the coefficient of variation of the duplicates - determined using the reference method – was below 4 %.

4.5. Determination of glucose concentration using test strips

For use of original unchanged blood samples, capillary blood was taken directly from the fingertip to get contact to the test strip.
For reference measurements, blood was sampled into Lithium Heparin tubes (Mikrovetten®, 300 µl were divided into 150 µl aliquots). The reference measurements using the Cobas apparatus were performed in plasma samples.

Sampling was performed in the following order:

1. 300 µl of blood were taken from the fingertip into Lithium Heparin tubes for reference measurement (samples were divided into aliquots of 150 µl each). The first reference sample (R1) was analysed directly after sampling.
2. BGM measurements:
   Tyson Bio HT-100 – GC 1 Lot 1
   Tyson Bio HT-100 – GC 2 Lot 1
   Tyson Bio HT-100 – GC 1 Lot 2
   Tyson Bio HT-100 – GC 2 Lot 2
   Tyson Bio HT-100 – GC 1 Lot 3
   Tyson Bio HT-100 – GC 2 Lot 3
3. Analysis of the second reference sample (R2) using the reference method (Cobas)
4. Blood sampling for determination of the hematocrit.

To get samples in the different by ISO defined ranges, the glucose concentration of any taken samples was adjusted in accordance with the instructions of DIN EN ISO 15197:2015 (blood spiked or blood stored). The spiked blood samples were safety mixed by rotation for 30 minutes at room temperature. Thereafter, an aliquot was taken for Cobas reference measurements before and after BGM testing.

To get glucose concentrations < 80 mg/dl, blood samples were incubated at 37°C in a shaking water bath for 1 – 3 hours (stored) to be measured thereafter similar to the spiked samples.

5. Analysis / Results

5.1. Time of realization

The study was performed between 27th of June and 9th of July 2018.

5.2. Data

A total of 100 patient sample data which fulfilled the inclusion criteria, were included in the statistical analysis.
The complete data sets of the study are given in the Excel tables.

5.3. Analysis of system accuracy in accordance with DIN EN ISO 15197:2015 [1]

The analysis of data for the proof of system accuracy was done in accordance with the instructions given in the DIN EN ISO 15197:2015 [1]. The test measurements were compared with the reference values determined using the Cobas C111 system.
For samples with concentrations <100 mg/dl the deviation of test values from the mean of the reference values were calculated in mg/dl. For samples with glucose concentrations >100 mg/dl the percentage deviation form the mean of the reference values were calculated.

The following parameters were calculated:

Drift in %	deviation of the reference values from Cobas values in %
Cobas average	mean of reference values in mg/dl
Dev. GC to Cobas in mg/dl	average deviation of the measured values to the reference value in mg/dl
Dev. GC to Cobas in %	average deviation of the measured values to the reference value in %

Result of system accuracy of Tyson Bio HT-100 for glucose concentrations <100 mg/dL

	within ± 5mg/dL	**within ± 10mg/dL**	**within ± 15mg/dL**
Lot 1	25 / 48 (52.1 %)	44 / 48 (91.7 %)	48 / 48 (100 %)
Lot 2	27 / 48 (56.3 %)	45 / 48 (93.8 %)	48 / 48 (100 %)
Lot 3	24 / 48 (50.0 %)	41 / 48 (85.4 %)	48 / 48 (100 %)
Lot 1, 2 and 3 in summary	76 / 144 (52.8 %)	130 / 144 (90.3 %)	144 / 144 (100 %)

Result of system accuracy of Tyson Bio HT-100 for glucose concentrations ≥100 mg/dL

	within ± 5%	**within ± 10%**	**within ± 15%**
Lot 1	99 / 152 (65.1 %)	134 / 152 (88.2 %)	149 / 152 (98.0 %)
Lot 2	78 / 152 (51.3 %)	127 / 152 (83.6 %)	145 / 152 (95.4 %)
Lot 3	75 / 152 (49.3 %)	131 / 152 (86.2 %)	149 / 152 (98.0 %)
Lot 1, 2 and 3 in summary	252 / 456 (55.3 %)	392 / 456 (86.0 %)	443 / 456 (97.2 %)

System accuracy of Tyson Bio HT-100 for combined glucose concentrations

	within ± 15 mg/dL or 15%
Lot 1	197 / 200 (98.5 %)
Lot 2	193 / 200 (96.5 %)
Lot 3	197 / 200 (98.5 %)
Lot 1, 2 and 3 in summary	587 / 600 (97.8 %)

In all three test strip lots more than 95 % of the readings had a deviation to the reference method of less than 15 % (for values >100 mg/dl) or of less than 15 mg/dL (for values <100 mg/dl) respectively. The Tyson Bio HT-100 in all three test strip lots fulfilled the criteria of the quality norm DIN EN 15197:2015 .
A regression analysis was performed according to Passing and Bablok [4] and the readings are shown in the Error Grid Diagram.

Figure 1: Error Grid Analysis of test Lot 1 (MSH022G006),
Mean values of Tyson Bio HT-100. vs. mean values of the Cobas C111

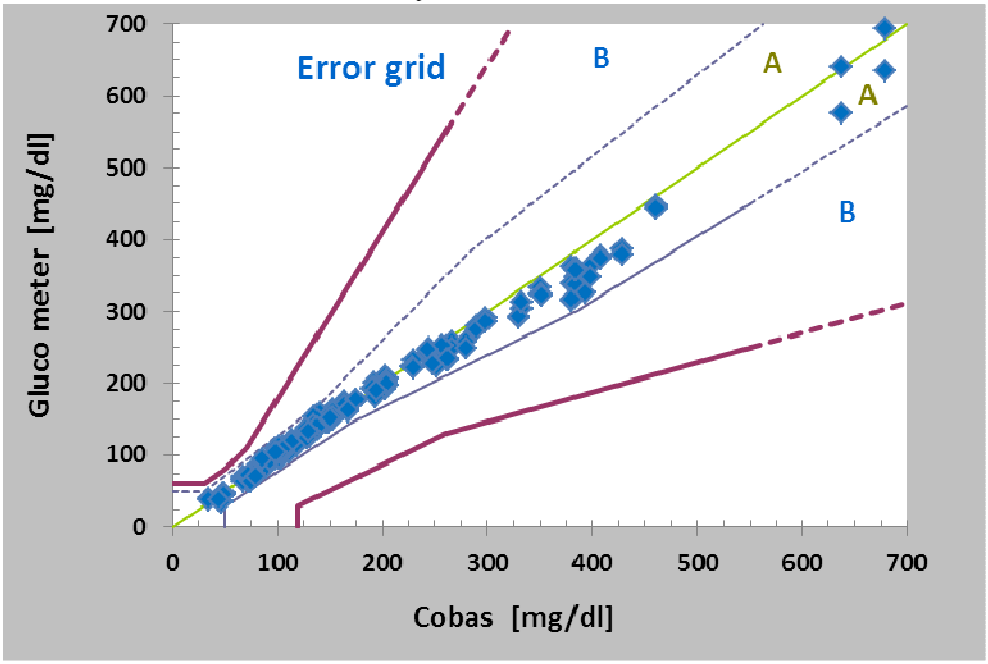

Figure 2: Graphic representation of the differences between the Tyson Bio HT-100
(Lot 1) and reference measurements, as a function of the glucose concentration

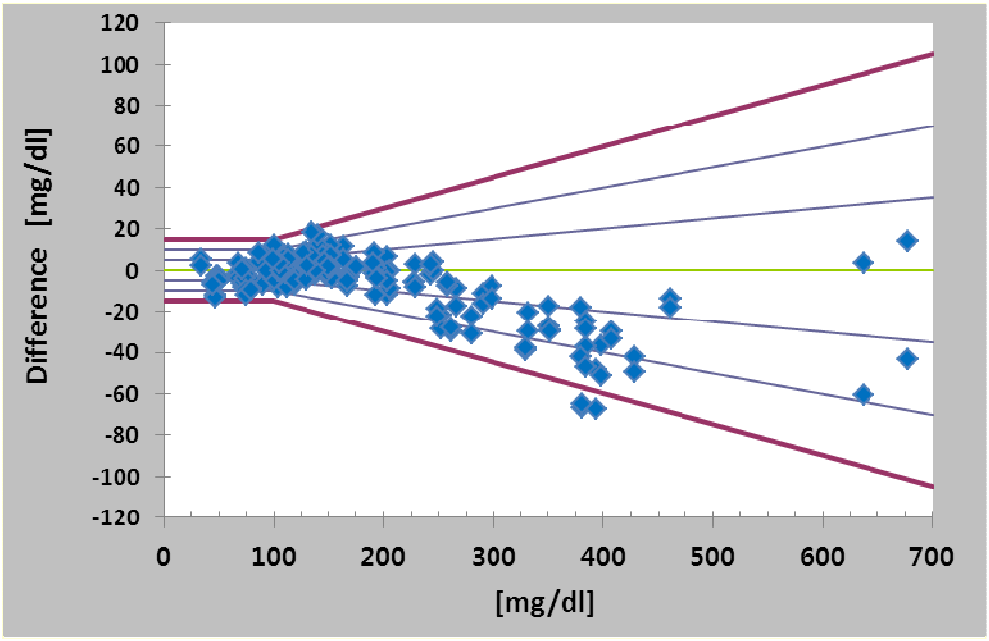

Figure 3: Error Grid Analysis of test Lot 2 (MSH022G008),
Mean values of Tyson Bio HT-100 vs. mean values of the Cobas C111

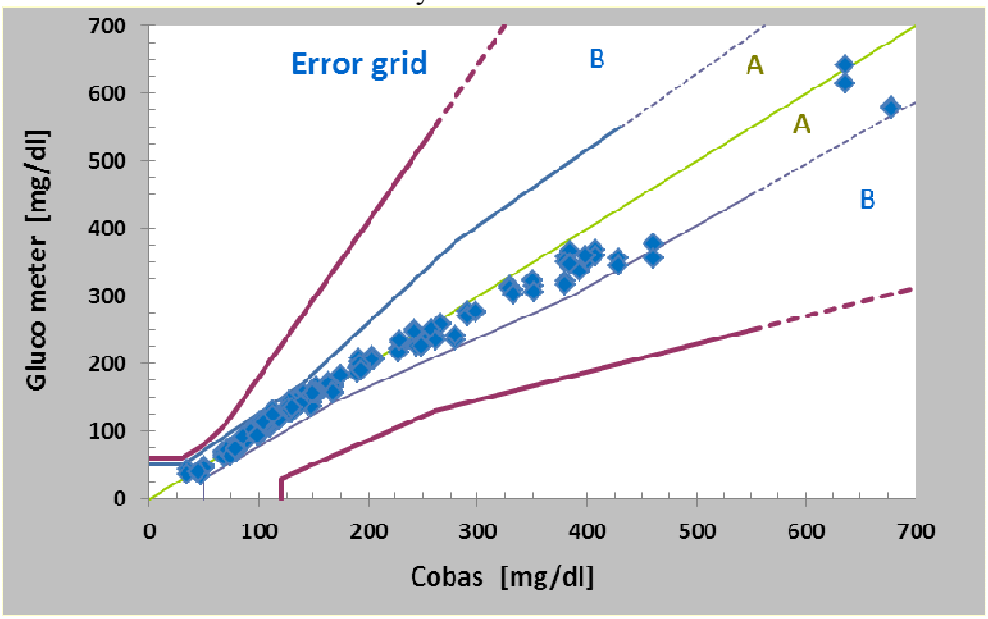

Figure 4: Graphic representation of the differences between the Tyson Bio HT-100 (Lot 2) and reference measurements, as a function of the glucose concentration

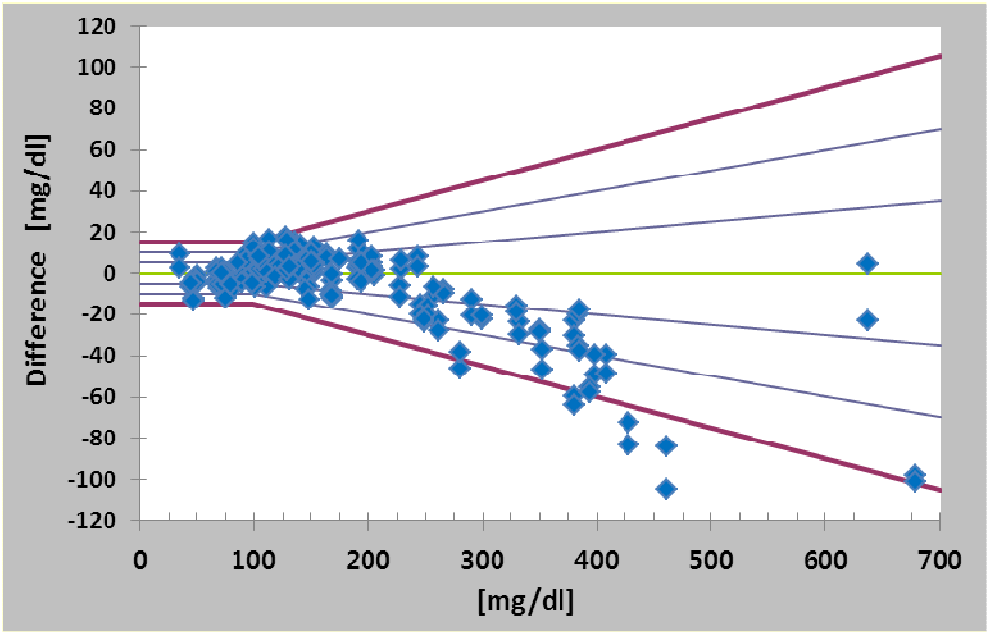

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Figure 5: Error Grid Analysis of test Lot 3 (MSH022G066),
Mean values of Tyson Bio HT-100 vs. mean values of the Cobas C111

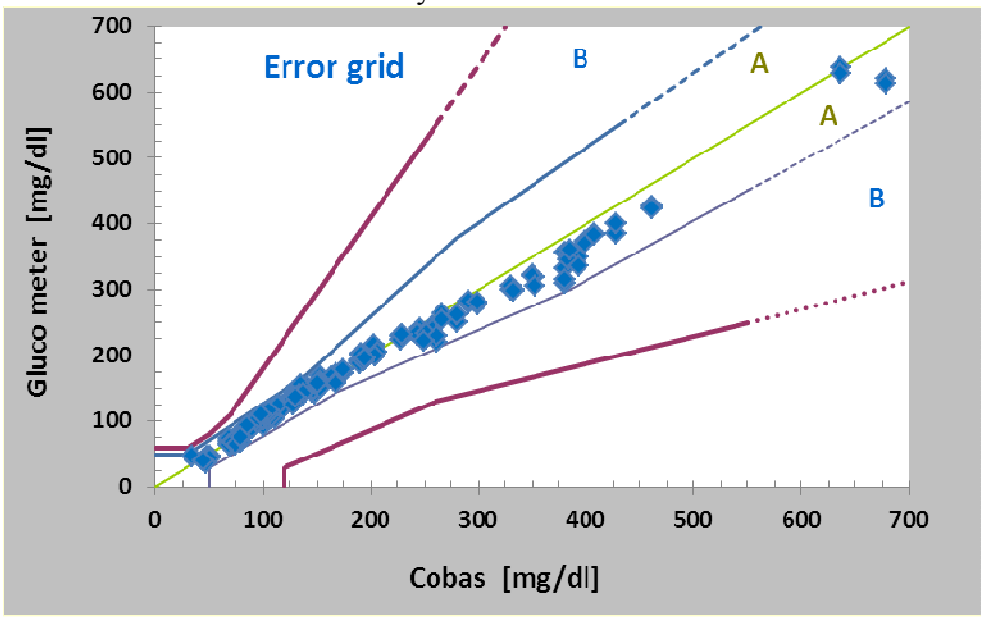
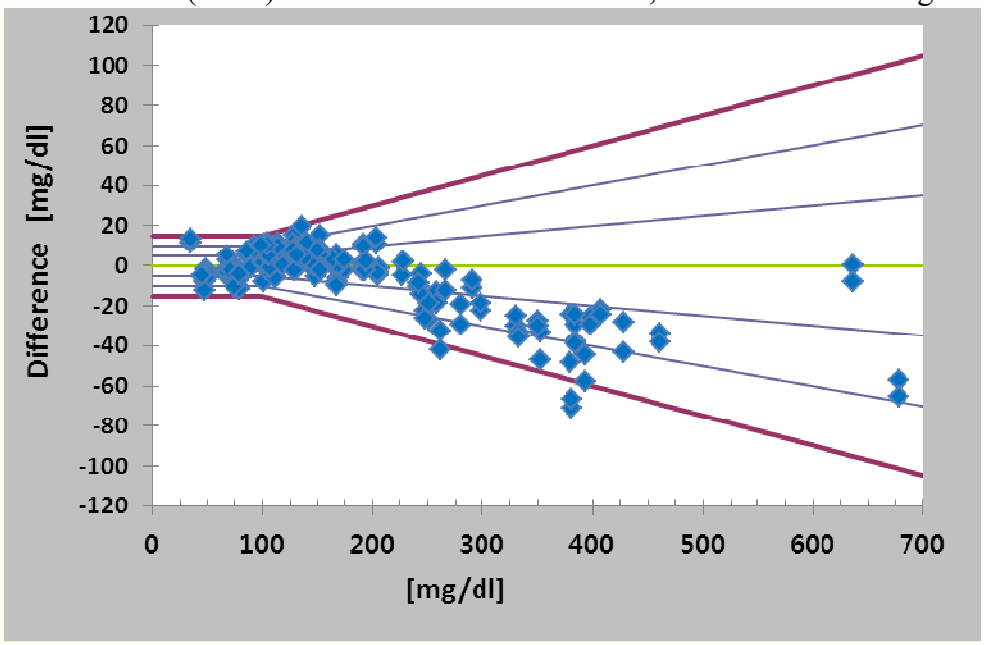


Figure 6: Graphic representation of the differences between the Tyson Bio HT-100 (Lot 3) and reference measurements, as a function of the glucose concentration



The readings of all three test lots were within the region A and B of the Parkes Error Grid.

6. Summary and conclusions

The criteria for the system accuracy according to the standard DIN EN ISO 15197:2015 were fulfilled for the blood glucose monitoring system Tyson Bio HT-100:

- 100 % of the performed measurements were within the zone A and B of the Consensus Error Grid [5].
- According to the results of system accuracy 97.8 % of all measurements were within the required range.
- For the Tyson Bio HT-100 system, the criteria of the DIN EN ISO 15197:2015 were met by the study data.

References

1. Testsysteme für die In-vitro-Diagnostik – Anforderungen an Blutzuckermesssysteme zur Eigenanwendung beim Diabetes mellitus (DIN EN ISO 15197:2003)

2. Testsysteme für die In-vitro-Diagnostik - Anforderungen an Blutzuckermesssysteme zur Eigenanwendung bei Diabetes mellitus (DIN EN ISO 15197:2015).

3. Bland J.M. and Altman D.G.: Statistical methods for assessing agreement between two methods of clinical measurement. Lancet 1986, 307-310.

4. Passing H. and Bablok W.: A new biometrical procedure for testing the equality of measurements from two different analytical methods. J Clin Chem Clin Biochem Vol. 21, 1983: 709-720.

5. Parkes J.L., Slatin S.L., Pardo S., Ginsberg B.H.: A New Consensus Error Grid to Evaluate the Clinical Significance of Inaccuracies in the Measurement of Blood Glucose. Diabetes Care 2000. 23:1143–1148.

Signatures

The undersigned has reviewed the format and content of this report.

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