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The quality of blood glucose meters in the Netherlands 5 years after introduction of the CE/IVD directive

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The introduction in Europe of the mandatory and only forcible by law Conformité Européenne (CE)/In-Vitro Diagnostica(IVD)-directive for testing bloodglucose-meters (BGMs) has created a quality problem. Before 2001 most BGMs were accredited in the Netherlands according to the TNO quality guideline for testing BGMs [1]. TNO is the Netherlands organisation for applied scientific research. Nowadays, the TNO guideline is still one of the most stringent and most extensive guidelines for testing BGMs.

The CE/IVD directive is not sufficient or incomplete for a number of reasons:

- Obtaining a CE-label for BGMs is a one-time process after which a yearly monitoring of the quality is not mandatory.
- The minimal volume of the blood droplet used for analysis to obtain a correct result is not evaluated under this CE/IVD directive itself and also not as part of ISO 15197 for BGMs. Underfilling protection is not necessary to obtain a CE-label. The only requirement is that the manufacturer specifies what minimal quantity of blood should be used.
- Manufacturers do not have to follow ISO 15197. The CE/IVD directive only prescribes that what is stated by the manufacturer must be proven by the manufacturer. In principal this is sufficient to obtain a CE-label on a BGM.
- Moreover, even if the ISO 15197 is followed, the manufacturers may define their own reference method. As a consequence the results of glucose measurements may deviate more than 20% from a hexokinase ID-GCMS aligned method. The hematocrit dependency may enlarge this deviation in some patients even more.
- A method comparison based on the acceptance of 20% deviation as described in ISO 15197 is not sufficient. The TNO-criterium of 15% against a defined reference method is better but still insufficient [2-5].
- The CE/IVD directive does not verify the hematocrit range claimed by the manufacturer. It is impossible for patients without good laboratory facilities to check the statements made by the manufacturers.

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Methods

30 CE-labeled glucosemeters available on the Dutch market (Table 1) were tested according to the TNO quality quideline with respect to accuracy, reproducibility and haematocrit dependency. Moreover, CE-labeled meters were tested whether or not they had a protection against producing wrong results at underfilling. The meters were tested in Zwolle and in Amsterdam seperately. Testing was done by experienced technicians. The hexokinase method was used as the reference method. This study was performed as a blinded study. This was done because all manufacturers of the tested BGMs meet the requirements of the official CE-guideline.

Accuracy

50 patients were tested bedside. Several meters were tested simultaniously. Capillary blood was taken for the reference method. A minimum of 10 patients was needed with glucose <6.5 mmol/L.

The accuracy performance criteria according to the TNO guideline are such that 95% of the capillary whole blood glucose values, ranging from the lowest to the highest measurable value specified by the manufacturer shall:

- for a level of ≥ 6.5 mmol/L, amount to a maximum of ± 15% relative to the average value as obtained with the hexokinase method (reference laboratory method),
- for blood glucose values < 6.5 mmol/L to a maximum of ± 1.0 mmol/L,

Reproducibillity

Venous whole blood (lithium-heparine) from 10 patients was used. A minimum of 3 patients was needed with glucose <6.5 mmol/L. Blood glucose was measured in 10-fold, within 30 minutes. The reference method was used before and after the reproducibility test.

The allowable coefficient of variation of ten independent observations is ″ 5% at blood glucose values? 5.0 mmol/L or ″ 0.5 mmol/L at blood glucose values < 5.0 mmol/L. One of these ten results is allowed to be outside this requirement.

Haematocrit dependency

Venous blood from 5 patients was used. The glucose concentration was adjusted if needed to get glucose values from 2 - 22 mmol/L. Different haematocrits were prepared by adding or removing plasma. Glu-

cose was measured with the BGM and the reference method. Results were corrected for systematical deviation between the BGM and the reference method.
The variation in the blood glucose value as a result of variation of haematocrit values (range stated by the manufacturer) of venous whole blood may amount to no more than 10% over the whole range at blood glucose (reference method) values ≥ 6.5 mmol/L and may amount not more than 1.0 mmol/L at blood glucose values < 6.5 mmol/L. The minimum range for the haematocrit prescribed by the TNO guideline is 0.35 - 0.50 (L\L) (35% - 50%). If the manufacturers range is larger this range was also investigated.

Droplet volume
Venous blood from a minimum of two patients was collected and pooled. Glucose values were 8 - 12 mmol/L. 10-fold measurements were performed at three droplet volumes:
- test surface covered completely or acoording to manufacturer's specifications (size A)
- smallest size when a measurement is posssible
- size at which the measurement will not start

The mean from the run with size A was calculated and for the other sizes, difference with this figure were calculated.
With the smallest droplet that still gives a result, CV must be <10%. If the volume of the blood droplet on the reagent system is not sufficient for measurement, the measurement procedure may not be possible, a warning or error indication should be issued. When a value is given, the value may alter not more than 10%.

Table 2. Results of 30 CE-labeled bloodglucosemeters for patient use which were tested according to a limited number of criteria derived from the TNO guideline

Test performed	Results based on TNO criteria
Accuracy (max. 15% deviation from hexokinase-method)	60% passed
Reproducibility (max. CV 10%)	83% passed
Haematocrit dependency (range 0.35 - 0.50 L/L) (max CV 10% at maximum for glucose values < 6.5 mmol/L or 1 mmol/L for glucose values < 6.5 mmol/L)	83% passed
Haematocrit dependency range stated by manufacturers	17% passed
Underfilling protection (max 10% from result at minimal volume or error mark)	20% passed

Table 1. CE-labeled blood glucosemeters tested in this study. Data obtained in this study were anonymised in such a way that data were not traceable to the blood glucosemeters.

Bloodglucosemeter	Manufacturer
Accu-Check Active	Roche Diagnostics GmbH, Mannheim, Germany
Accu-Check Advantage	Roche Diagnostics GmbH, Mannheim, Germany
Accu-Check Aviva	Roche Diagnostics GmbH, Mannheim, Germany
Accu-Check Compact Plus	Roche Diagnostics GmbH,Mannheim, Germany
Accu-Check Go	Roche Diagnostics GmbH, Mannheim, Germany
Ascensia Breeze	Bayer HealthCare LLC, Mishawaka, USA
Ascensia Contour	Bayer HealthCare LLC, Mishawaka, USA
Ascensia Elite	Bayer HealthCare LLC, Mishawaka, USA
Balance Olympia	Balance B.V. 's-Hertogenbosch, Netherlands
BD Logic	Becton Dickinson, Franklin Lakes, USA
Easy Check	Tai Doc Technology Corporation, Taiwan
Easy Gluco	Infopia Co., Ltd, Korea
Eusure	Eumed Biotechnology Co., Ltd, Jubei City,Taiwan
EZ Smart	Tyson Bioresearch, Inc, Taiwan
FreeStyle Mini	Therasense Inc. Almada, USA
Gluco Smart +	MSP bodmann GmbH, Oberottmarshausen, Germany
Glucocard X-Meter	Arkray, Inc.,Kyoto, Japan
GlucoLeader Enhance	HMD Biomedical Inc. Hsinchu, Taiwan
GlucoMen Glyco	A.Menarini Diagnostics Italy
GlucoTouch	LifeScan, Milpitas, USA
HemoCue Monitor	HemoCue AB, Ängelholm, Sweden
IME-DC	Int. Medical Equipment Diabetes Care, Oberkotzau, Germany
Multi Care	Biochemical Systems International s.r.l, Arezzo, Italy
MWD Pen Sensor	All Medicus co., Ltd, Korea
Omnitest Sensor	B.Braun Petzold GmbH, Melsungen, Germany
On Call Now	Acon Laboratorios, Inc. San Diego, USA
One Touch Ultra	LifeScan, Milpitas, USA
Precision Xceed	MediSense UK Limited; United Kingdom
SensoLite Nova	77 Elektronika Co., Ltd, Budapest, Hongaria
Wellion True Track	Home Diagnostics Inc, Fort Lauderdale, USA

Results
The results are presented in table 2.

Conclusion
In conclusion, less then 20% of the evaluated BGMs met the tested criteria of the TNO guideline. Therefore, we propose an extension of the CE/IVD-directive with respect to the quality of glucose measurement to avoid misleading CE labeling of BGMs. The quality criteria defined will need to be at least as strict as those defined by the TNO guideline. Furthermore a yearly check of all the BGMs in the market is needed to assure ongoing quality of blood glucose meters. A protection against underfilling is warranted.

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Metabole ratio's van psychofarmaca als indicatie voor het cytochroom-P450-genotype: klinische toepassingen

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Behandeling met antidepressiva en antipsychotica wordt gekenmerkt door grote individuele verschillen in respons en de benodigde dosis. Een belangrijke oorzaak hiervoor is de individuele variatie in metabole capaciteit, die wordt veroorzaakt door variatie in activiteit van cytochroom-P450(CYP)-enzymen. Voor het metabolisme van psychofarmaca zijn vooral CYP1A2, 2C9, 2C19, 2D6 en 3A4 van belang. De activiteit van deze enzymen wordt zowel bepaald door endogene factoren zoals leeftijd, geslacht, morbiditeit en genetische samenstelling, als exogene factoren zoals co-medicatie, voedsel en rookgewoonten (1). Het voorkomen van genpolymorfismen bepaalt in belangrijke mate de individuele variatie in CYP-activiteit. Dit houdt in dat er minder en meer actieve CYP-fenotypen in een populatie voorkomen, doordat er verschillende allelen van het gen zijn. Hoewel de meeste CYP-enzymen polymorfisme vertonen, zijn er tot op heden alleen klinisch relevante polymorfismen van CYP2C9, 2C19 en 2D6 gevonden. Van CYP2D6 zijn intussen meer dan 90 polymorfismen aangetoond die in meer of mindere mate een klinisch relevante betekenis hebben voor het metabolisme van psychofarmaca (http://www.cypalleles.ki.se/cyp2D6.htm). Naast het wildtype, zijn er nulmutaties, waarbij een deficiënt enzym wordt gevormd, partiële mutaties, waarbij een deels functioneel enzym wordt gevormd, en genamplificaties, waarbij meerdere kopieën van het *CYP2D6*-gen resulteren in een toename van de totale hoeveelheid actief enzym (1). Op basis van de verschillende genotypen kan traditioneel onderscheid worden gemaakt in langzame metaboliseerders (PM), die twee deficiënte allelen bezitten, intermediaire metaboliseerders (IM), die heterozygoot zijn voor een deficiënt allel of twee deels functionele allelen bezitten, normale metaboliseerders (EM), die twee functionele allelen bezitten, en snelle metaboliseerders (UM), die meerdere genkopieën bezitten. Er is een duidelijk verband tussen de verschillende genotypen en de metabole ratio (MR) van testdrugs en psychofarmaca (2). Veel psychofarmaca hebben een relatief smal therapeutisch venster, waarbij bijwerkingen al kunnen optreden bij nauwelijks hogere concentraties. De therapeutische activiteit en bijwerkingen van een psychofarmacon worden dus in belangrijke mate beïnvloed door het genotype van het metaboliserende enzym. Van langzame metaboliseerders is aangetoond dat ze meer psychofarmaca-gerelateerde bijwerkingen hebben, terwijl er vaker van medicatie wordt geswitcht en de gemiddelde opnameduur langer is in vergelijking met normale metaboliseerders (3). Het therapeutische effect van een psychofarmacon is vaak pas enkele weken na de start van de therapie zichtbaar. Tijdens deze periode kan de therapeut niet vaststellen of het middel aanslaat, terwijl de klachten van

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