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Systematic monitoring of standardization and harmonization status with commutable EQA-samples—Five year experience from the Netherlands

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ABSTRACT

Background: Equivalence of results among laboratories is a major mission for medical laboratories. Monitoring of test equivalence is structurally integrated in the Dutch External Quality Assessment (EQA) scheme since 2005. Commutable poolsera, single donation "spy" sera and biological variance tolerance limits have been introduced in the EQA scheme for evaluation of the degree of test equivalence and its determinants.
Methods: In the annual cycle scheme 24 samples, covering the (patho)physiological measuring range for 17 analytes, are assayed by 220 participating laboratories at biweekly intervals. Test equivalence was evaluated by calculating overall median interlaboratory coefficients of variation (CVs) and its bias and imprecision components. Data from 2005 and 2010 schemes are evaluated to investigate trends in performance and success of standardization efforts.
Results: Overall median interlaboratory CVs in 2010 were mostly better than in 2005. Median interlaboratory CVs became <5% for electrolytes and substrates, and <10% for enzymes. Improvement in median interlaboratory CVs over these five years is mainly explained by improved method standardization, especially for enzymes and creatinine.
Conclusion: The Dutch EQA-program proves to be a powerful instrument to evaluate test equivalence. It allows monitoring standardization efforts in a highly effective way and gives insight into remaining standardization potential.

1. Introduction

Interchangeability of laboratory test results across laboratories and time is a major topic in laboratory medicine and can be achieved by either standardization or harmonization [1–4]. The degree of interchangeability or test equivalence and the success of standardization/harmonization efforts can be monitored by external quality assessment (EQA) schemes, also known as proficiency testing programs [4]. Major advantages of using EQA schemes are that these a) reflect real life analytical conditions as ideal research circumstances are avoided, b) provide robust data as many labs and many methods are included and c) can be organized efficiently without requiring separate evaluations for monitoring harmonization/standardization. To be an effective monitoring tool for assessing traceability, EQA schemes should meet at least two fundamental requirements. Firstly, the EQA-specimens used should be commutable—i.e. behave like native patient materials—to prevent that differences seen are related to matrix effects rather than to differences between methods. Secondly, the target value should, whenever feasible, preferentially be assigned by JCTLM-listed reference laboratories with approved reference systems. Value assignment can be done either directly with a reference measurement procedure or a designated comparison method, or indirectly by anchoring the assigned value to a certified reference material under the condition that transferability is guaranteed. In addition biological variance based tolerance limits should be used. According to the Stockholm consensus conference on quality specifications in

Abbreviations: CV, coefficient of variation; EQA, external quality assessment; IVD, in vitro diagnostic; JCTLM, Joint Committee on Traceability in Laboratory Medicine; SKML, the Dutch EQA, named Stichting Kwaliteitsbewaking Medische Laboratorium Diagnostiek; TE_a, allowable total error.

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laboratory medicine [5], EQA consensus results are on the 5th level of its hierarchy and biological variation based criteria on its 2nd level. EQA schemes in other countries have set Minimal Allowable Performance limits, sometimes based on consensus group mean values and tolerance limits based on e.g. 95th percentile of results [6], other based on biological variation [7]. However, no information on the commutability of the samples used is given.

SKML (Stichting Kwaliteitsbewaking Medische Laboratorium Diagnostiek), the EQA provider in the Netherlands, organizes EQA schemes meeting these requirements since 2005 [8–18]. In addition, SKML integrates standardization and harmonization efforts since 1998 under the flagship of Calibration 2000 for analytes with unacceptable bias in the EQA scheme [11–15,18]. Thirdly, a scoring system was developed based on biological variation. In this paper national general clinical chemistry data of the EQA schemes in 2005 and 2010 are compared for 17 parameters to investigate a) whether analytical performances have improved, b) whether standardization efforts have been successful and c) whether there is room for further improvement of equivalence. For medical lab professionals these data are an appropriate means to verify if the in vitro diagnostic (IVD)-industry meets the IVD directive 98/79/EC. This European directive obliges manufacturers to produce kits with traceable measurement results and documented uncertainty. The aggregated data in this paper allow evaluating if the present IVD-kits indeed meet the medical needs. And when not, whether better quality can be achieved by more strict standardization or that intrinsically better methods are required to achieve quality goals.

2. Materials and methods

2.1. Specimens

Samples (N = 24) are prepared from fresh, anonymized left-over sera of the routine clinical chemistry laboratory with exclusion of icteric and lipemic samples. Left-over sera are tested for HBsAg, a-HIV and a-HCV and negative sera are stored frozen at −84 °C in aliquots of 200 mL. The use of anonymous left-over sera is in accordance with national guidelines on acceptable use of body fluids, and does not demand informed patient consent.

Prior to manufacture of the EQA samples the aliquots are thawed and pooled. Physiological and pathophysiological concentration ranges are created by adequately mixing pools and by spiking with minerals, recombinant human enzymes and human albumin. The concentration ranges that are systematically tested are presented in Table 1. After dispensing, vials are frozen at −84 °C until shipment to the participants. At the beginning of the annual cycle samples are shipped on dry ice to the participants who store them at −84 °C until analysis. Commutability of the Dutch EQA-samples has been established [16–19], and reference [14] with proof of commutability for 17 analytes, has been translated and summarized in an attached supplemental file. Throughout the years commutability has been monitored by including a native, single donation spy-sample that is prepared according to NCCLS C37-A2.

2.2. Target value assignment

Target values are set by JCTLM-endorsed Reference Laboratories using approved reference measurement procedures (www.bipm.org) in 13 out of 17 general chemistry analytes. Value assignments are systematically done in the low and the high pools for 13 constituents. The in-between levels are manufactured by mixing high and low pools in different amounts. The latter procedure allows calculating the target values for the in-between levels. Table 1 lists the respective general clinical chemistry analytes, the reference or definitive measurement procedures and the involved reference laboratories.

2.3. EQA-design

Since 2005 the Dutch EQA-scheme has used an EQA-toolbox, consisting of commutable, value-assigned EQA-materials and a scoring system based on biological variation, for monitoring metrological traceability.

The EQA scheme is framed in an annual cycle with 12 blinded samples measured for 17 parameters at two-weekly intervals in the first half year, and 12 blinded duplicate samples measured at two-weekly intervals in the second half year. By covering the physiological and pathophysiological concentration range twice for each parameter, the design allows to investigate duplicability, linearity and recovery.

Table 1
Clinical chemistry parameters tested in the Dutch EQA on analytical performance trends between 2005 and 2010.

Analyte		Symbol	Concentration range	Reference methods	Reference laboratory
Minerals	Calcium	Ca^{2+}	1.77–3.27 mmol/L	Atomic absorption spectrometry	INSTAND e.V., Düsseldorf, Germany
	Chloride	Cl^{a}	83–116 mmol/L	Coulometry	INSTAND e.V., Düsseldorf, Germany
	Magnesium	Mg^{2+}	0.59–2.01 mmol/L	Atomic absorption spectrometry	INSTAND e.V., Düsseldorf, Germany
	Potassium	K^{+}	3.2–7.8 mmol/L	Flame emission spectrometry	INSTAND e.V., Düsseldorf, Germany
	Sodium	Na^{+}	118 − 167 mmol/L	Flame emission spectrometry	INSTAND e.V., Düsseldorf, Germany
Substrates	Creatinine	Crea	54–262 μmol/L	GC-IDMS	DGKL, Bonn, Germany
	Glucose	Glu	3.9–30.0 mmol/L	GC-IDMS	INSTAND e.V., Düsseldorf, Germany
	Total Protein	TE	49–82 g/L	Modified Biuret Method	INSTAND e.V., Düsseldorf, Germany
	Uric Acid	UA	0.22–0.58 mmol/L	HPLC	Erasmus Medical Centre, Rotterdam, Netherlands
Enzymes	ALT	ALT	17–214 U/L (at 37 °C)	IFCC primary reference method; Clin Chem Lab Med 2002;40:718-24	Haga Hospital, The Hague, The Netherlands
	AST	AST	18–147 U/L (at 37 °C)	IFCC primary reference method; Clin Chem Lab Med 2002;40:725-33	Haga Hospital, The Hague, The Netherlands
	γ-GT	GGT	30–175 U/L (at 37 °C)	IFCC primary reference method; Clin Chem Lab Med 2002;40:734-38	Haga Hospital, The Hague, The Netherlands
	LDH	LDH	116–1143 U/L (at 37 °C)	IFCC primary reference method; Clin Chem Lab Med 2002;40:643-48	Haga Hospital, The Hague, The Netherlands
Consensus	Albumin	Alb	31–71 g/L	Consensus value = Mean laboratories	Not applicable
	Alkaline Phosphatase	AP	55–272 U/L (at 37 °C)		
	Phosphate	P	0.8–2.5 mmol/L		
	Urea	Urea	4.6–28.9 mmol/L		

The Dutch EQAS uses human, fresh frozen and commutable sera since 2005 [12–15]. Analytes in the EQA scheme are categorized into analytes for which reference measurement procedures were used to set target values (with subdivision for minerals, substrates, and enzymes, respectively; N = 13) and analytes for which no reference measurement procedures are available and for which consensus values are used as target values (consensus; N = 4). Categories as well as symbols listed here are used throughout the paper, especially in the figures. Reference Methods and Reference Laboratories involved with value assignment are listed.