Quality Assessment of CoaguChek Point-of-Care International Normalized Ratio Monitors: A Note of Caution

To the Editor:

In a recent publication Poller et al. (1) described quality assessment (QA) of CoaguChek (CUC) point-of-care (POC) international normalized ratio (INR) monitors and compared 2 procedures. The study compared the proportion of 523 CUC monitors having unsatisfactory performance as indicated by either a >15% deviation of INR results from the INR assigned to 5 lyophilized QA plasmas or a >15% deviation from the overall median of INRs obtained on the monitors included in the survey. The INRs assigned to QA plasmas had been derived from a full calibration in compliance with WHO-recommended procedures and a local mean normal prothrombin time.

The CUC device is calibrated by the manufacturer for use with non-anticoagulated whole blood. Patients using the device analyze whole blood and not plasma. Furthermore, the calibration procedure employed by Poller et al. (1) used whole blood samples to derive the International Sensitivity Index for assigning INRs to the lyophilized plasma samples. We believe that caution is required when interpreting data obtained on lyophilized plasma samples for devices calibrated for whole blood, and that results should not be assumed to be representative of results that would have been obtained for whole blood analysis.

We recently reported results for 6 years (1996–2002) of experience with external QA (EQA) of CUC and CUC-S devices, comparing >30 test samples analyzed by up to 175 centers (2). We have continued to perform EQA surveys and recently analyzed data on 8 different freeze-dried plasma samples obtained in 2006 from >800 centers, grouping results according to the lot number of test strips used for analysis. For several hundred test-strip lots used for a series of surveys, no significant difference was observed between results obtained with different lots, with 4 exceptions. On these 4 occasions, results with 1 lot number were >10% different from the median of results with all other lots. For 2 of these lots, test strips were available for further investigation. Native whole blood samples from warfarinized patients were analyzed to assess whether the discrepancy observed in lyophilized plasmas was also present when whole blood samples were analyzed. On the 1st occasion a series of lyophilized plasmas and native (non-anticoagulated) blood samples were analyzed with test strips from 2 different lots, including those for which the lot number was associated with the discrepancy identified in survey data. The plasma and whole blood samples were from different patients. For whole blood analysis, we collected samples by syringe, immediately applied them to strips from both lots, and analyzed them with 2 monitors. The mean INRs with the 2 lots were 3.08 and 3.79 (n = 12, 23% difference, P < 0.001) for lyophilized plasmas. For whole blood the mean INRs with the 2 lots were 2.75 and 2.96 (n = 10, 8% difference, P < 0.01).

On the 2nd occasion the mean INR of 10 lyophilized National External Quality Assessment Scheme (NEQAS) plasma samples was 3.97 with the lot number under investigation compared to a mean of 3.08 for samples analyzed by NEQAS participants using strips from multiple lots (29% difference, P < 0.001). Native blood samples from 14 patients were analyzed with the lot number under investigation and a 2nd lot number (which survey data had shown to be in agreement with other lots). The mean INRs for whole blood samples were 2.92 and 3.01 (3% difference, not significant) for these 2 lots. Thus the difference present when lyophilized plasmas were analyzed was absent when native whole blood was tested.

The reason for the different results for test strip lots for whole blood and lyophilized plasmas is unknown, but our data indicate that findings based on lyophilized plasma cannot be safely extrapolated to whole blood without supporting evidence.

On the basis of their study results, Poller et al. (1) concluded that a proportion of CUC monitors in current everyday use for dosage control gave unsatisfactory results. Our experience suggests that although this conclusion may be true for lyophilized plasmas, it should not be assumed that the same conclusion applies to whole-blood samples.

We believe that EQA for POC INR devices should be mandatory, as it is for laboratory INR methods. For large multicenter surveys (1, 2), EQA cur-
rently involves the use of lyophilized plasmas and can successfully identify genuine problems (2). EQA is useful to assess imprecision, to reassure users about the comparability of their results with those obtained by users of the same devices, and to promote good QA practices. We advise caution in the interpretation of such results. When such devices are calibrated only for analysis of whole blood, results for plasma cannot be used to assess accuracy without supporting evidence derived from whole blood analysis.

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References
2. Kitchen S, Kitchen DP, Jennings I, Woods TAL, Walker ID, Preston FE. Point-of-care International Normalised Ratios: UK NEQAS experience demonstrates necessity for proficiency testing of CoaguChek. The ECAA initially studied the reliability of use of plasma samples in calibrating the CoaguChek monitor (1) with an international sensitivity index (ISI). An optimum formulation of calcium chloride for recalcification of plasma on the CoaguChek and TAS monitors was developed for ISI calibrations and EQA. In full multicenter ISI calibrations at 10 centers, the plasma/whole blood ISI difference was thereby reduced to 1%–6% with various lots of CoaguChek test strips, but small differences between whole blood and plasma persisted. The ECAA studies also revealed previously unsuspected differences in mean ISI with different CoaguChek test strip lots (2). In full calibrations performed at 3 centers, 1 lot gave a 13% ISI difference (1.51) from the mean of 3 others (1.74). A similar interlot difference was detected with both whole blood and plasma. The ECAA EQA plasmas in our 2006 Netherlands national field study (3) also showed evidence of interlot differences. The relatively low detection rate of interlot problems reported by Kitchen and coworkers for the investigation of up to 70 different lots, of which only 4 showed >10% difference from the median INR, can be regarded only as evidence of the limitations of the UK NEQAS approach and the need for more specific EQA.

Kitchen and coworkers challenge our use of the whole blood ISI to certify the INR of ECAA EQA plasmas. The whole blood ISI was preferred because of the small but constant difference in ISI between plasma and whole blood that persisted even with our modified recalcification. Thus adoption of the whole blood INR certification seemed preferable because this method gives less deviation from the certified values without affecting the underlying principles of EQA, which are more concerned with variability than absolute truth.

The UK NEQAS is designed to cover the whole range of PT testing systems. Therefore it would be difficult to provide a similarly precise analysis of performance to that contained in the EC-approved Technology Implementation Plan designed specifically for the EQA of the CoaguChek. The ECAA Technology Implementation Plan specifies that users of point-of-care testing (POCT) monitors should test them with EQA plasmas at intervals of not >6 months (or whenever there is a change of the lot of test strips).

ECAA surveys showed that the POCT PT monitors are less precise than traditional methods and that a minimum of 5 INR-certified EQA plasmas tested on the same day was required in an exercise to provide a reliable EQA of CoaguChek monitors. Sets of 5 ECAA EQA plasmas are therefore provided to users with diluent and calcium chloride. A 15% or more deviation from certified INR on 1 or more test plasmas in the set of 5 is classified as “unsatisfactory performance” (4). Immediate EQA is thus provided for CoaguChek users.

Traditional UK NEQAS analysis is slower and different depending on deviation from the overall median of all participants in an exercise and taking weeks or months to provide the results for a user. The ECAA/ECAT Netherlands study in our 2006 report showed that the ECAA method of rapid, “on the spot” analysis by percentage deviation from certified INR values gave results similar to those of traditional UK