Commumativity of two JCTLM-listed secondary reference materials for two commercial lithium assays

To the Editor:

Bipolar disorders (BD) are a devastating illness, carrying a burden of both morbidity and all-cause mortality, including a high rate of suicides [1]. Lithium has been used for decades as a mood-stabilizing agent in the treatment of BD and other conditions with a manic component. Recent guidelines for the management of BD and acute mania continue to recommend the association of lithium with several atypical antipsychotics as first-line treatment options [2]. Therapeutic drug monitoring plays, therefore, an important role to determine the most effective dose for lithium and to avoid drug toxicity. Lithium exhibits a narrow therapeutic window, with toxic concentrations (>1.5 mmol/L) very near to the upper threshold for effective therapy (up to 1.2 mmol/L) [3]. Therefore, laboratories are expected to provide clinicians with accurate and comparable lithium results in order to correctly monitor the effectiveness of therapy and avoid patient’s intoxication.

In recent years, meaningful efforts toward standardization of measurements in Laboratory Medicine have been initiated by several organizations. Among others, the Joint Committee for Traceability in Laboratory Medicine (JCTLM) is an internationally recognized entity with the objective of identifying, through a review process, methods and materials that fulfill the definition of “higher order”. Particularly, the availability of suitable reference materials (RM) is a prerequisite for guaranteeing comparability of results among commercial assays. RM can be used for calibration of routine methods, but when RM are intended for direct value assignment to manufacturer’s calibrators, they should be extensively investigated for commutability. For serum lithium, the JCTLM database lists two matrixed RM, the lyophilized human serum-based BCR-304, provided by the Institute for Reference Material and Measurements (IRMM), and the frozen human serum Standard Reference Material (SRM) 956c from the National Institute of Standards and Technology (NIST).

In order to verify the suitability of these RM for use as secondary calibrators of the manufacturer’s selected measurement procedure, we tested their commutability using two commercially available assays measuring serum lithium by different analytical principles, i.e. direct potentiometry (Ion-Selective Electrodes (ISE) Direct, Roche Cobas Integra 400) and a colorimetric approach (Multigent Lithium, Abbott Architect c16000). A total of 27 leftover human serum samples (lithium concentrations, 0.24 mmol/L–1.15 mmol/L, Integra 400 values) were collected, aliquoted, and stored at −80 °C until their use. We measured lithium concentrations with the two systems in each biological sample, in SRM 956c (3 levels), and in BCR-304 in duplicate in two different runs. The BCR-304 was reconstituted according to the procedure recommended by the IRMM and the two analyzers were handled according to the manufacturer’s instructions. The manufacturer’s control materials were used to validate analytical runs. The commutability of RM was estimated from Deming regression analysis of the measured results in native samples using the 95% prediction interval (95PI) and multiples of the standard error of regression ($S_{y|x}$), in accordance with the CLSI C53-A standard [4].

The regression equation was: colorimetry = 1.078 (95% confidence interval (CI): 1.044 to 1.111) potentiometry − 0.010 mmol/L (95% CI: −0.034 mmol/L to 0.014 mmol/L) with $r$ = 0.9971. As shown in Fig. 1, the SRM 956c results did not fall inside the 95PI based on the results for the native clinical samples. In addition, using an acceptance criterion for commutability of ±3 times the experimental $S_{y|x}$ (±0.066), the relative residuals for SRM 956c (−2.956 for level 1, −4.044 for level 2, −3.209 for level 3) were all outside the acceptable range. BCR-304 results fall inside the 95PI, but its relative residual (−0.197) was outside the acceptable range, i.e. ±3 times the experimental $S_{y|x}$ for native samples.

Our results demonstrate that SRM 956c was not commutable between the evaluated methods. BCR-304 showed better, although not perfect, commutability and should be preferred to align lithium assays to higher-order references. According to its certified value (0.985 mmol/L ± 0.029 mmol/L), our results preliminarily showed a very good alignment for Abbott assay (mean BCR-304 results ± SD, 0.98 mmol/L ± 0.04 mmol/L); on the contrary the Roche method showed a negative bias (−6.6%) that possibly needs some verification.

The expanded combined uncertainty of BCR-304 (2.9%) is, however, relatively high and this may become an issue in fulfilling the goal of acceptable uncertainty of lithium measurements for clinical laboratories. With regard to the therapeutic drug monitoring, Fraser proposed an approach for determining acceptable analytic variation based on the half-life and dosing interval of the drug [5]. Assuming a time interval between doses of 12 h and a drug average half-life of 24 h, the goal of acceptable uncertainty (expanded) of lithium measurements for their clinical application (including the accumulated uncertainty of the corresponding
traceability chain and the uncertainty due to the random effects of measurement) using unbiased assays should stay within ±4.3% (desirable quality level). If BCR-304 is used in the traceability chain for lithium, it would leave only ~50% of the uncertainty budget for the remaining lower parts of the chain.

References