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# THE IMPACT OF UNCERTAINTY OF COMMERCIALLY AVAILABLE QUALITY CONTROL SPECIMENS FOR THE THERAPEUTIC DRUG MONITORING OF LAMOTRIGINE

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## INTRODUCTION

The therapeutic drug monitoring (TDM) of newer antiepileptic drugs allow to gain best efficacy in the treatment of many neurological and neuropsychiatric disorders. To this end, the application of quality control (QC) assures reliability of analytical results from unknown specimens by measuring the consistency of results from QC samples (QCS) against their target value. In order to simplify QC procedures, commercially available QCS for automated immunochemical assays have usually same target value across different production batches, that is achieved by laying 10% tolerance on lot-to-lot variability. Albeit apparently small, this potential uncertainty do affects the effectiveness of QC for it is generally unknown by the end-user.

## Methods

In our laboratory (Policlinico Umberto I, Rome – Sapienza University of Rome), the use of Sheweart Control Chart (SCC) showed a persistent positive bias within ±1sd for a turbidimetric Lamotrigine assay (QMS® Immunoassay, Thermo Fisher Scientific, Monza, Italy), that caused ineffective but costly corrective actions. To address the issue, a preliminary method comparison study against spectrophotometric test with semi-log calibration (ARK™ Diagnostics for Siemens Healthcare, Milano, Italy) was carried out on both real specimens (N=58) and QCS (N=42, i.e).

## Results

Passing-Bablok regression showed neither proportional nor systematic bias between the methods for both QCS and real samples. The same positive bias was eventually shown also in the spectrophotometric assay. Consequently, the QC procedure was changed by modifying the SCC whereby incorporating the uncertainty about the nominal value of the QCS that was assumed to be ±10%. Whereby this new device it was possible to avoid false-alarms due to bias between nominal and actual value of the QCS that laid within ±1sd on the SCC.

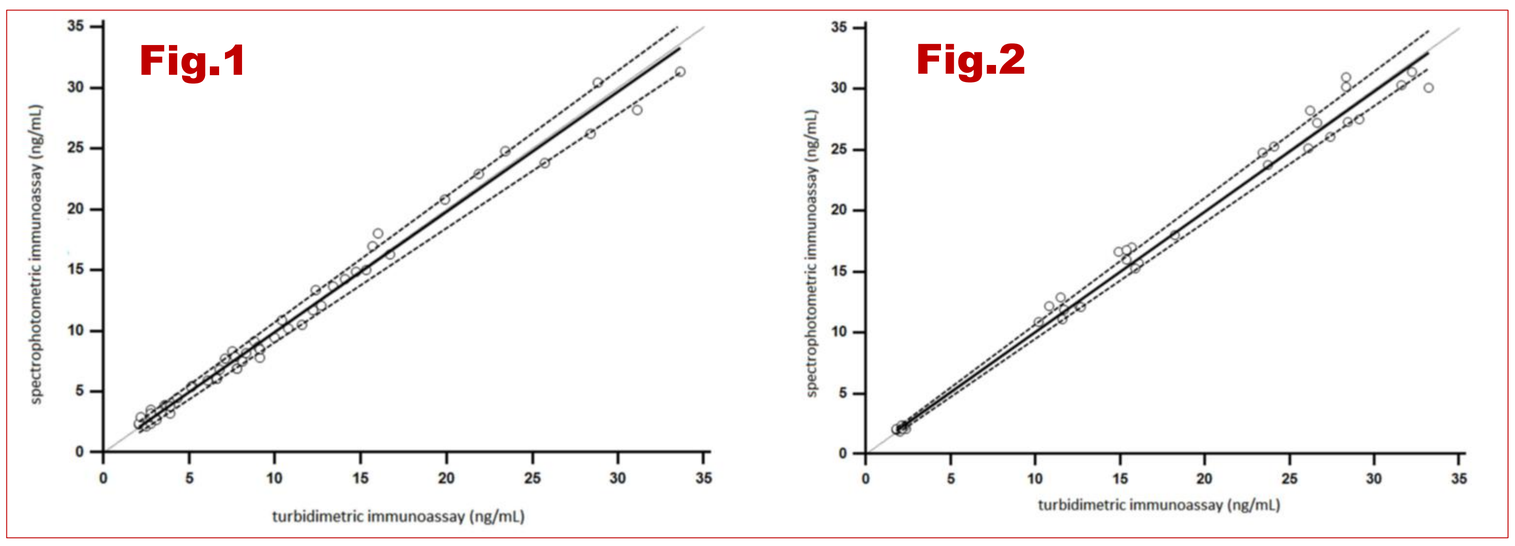





*Figure 1. Passing-Bablok regression analysis of real unknown samples of plasma Lamotrigine (N=58) by turbidimetric vs spectrophotometric assay on automated chemistry analysers*

*Figure 2. Passing-Bablok regression analysis of Quality Control samples (QCS) of plasma Lamotrigine (N=42) by turbidimetric vs spectrophotometric assay on automated chemistry analysers*

*Figure 3: Shewart Control Chart (SCC) with uncertainty about the target value T derived from uncertainty about the nominal value of the Quality Control Specimen (QCS); as it can be seen, the apparently systematic bias within the control limits is indeed derived from uncertainty about the actual value of the specimen that is affected by the tolerance of the QCS manufacturing process; this adjunctive control region prevents to consider the pattern of systematic deviations above the centerline as a bias in the methods that would prevent to run the analysis.*

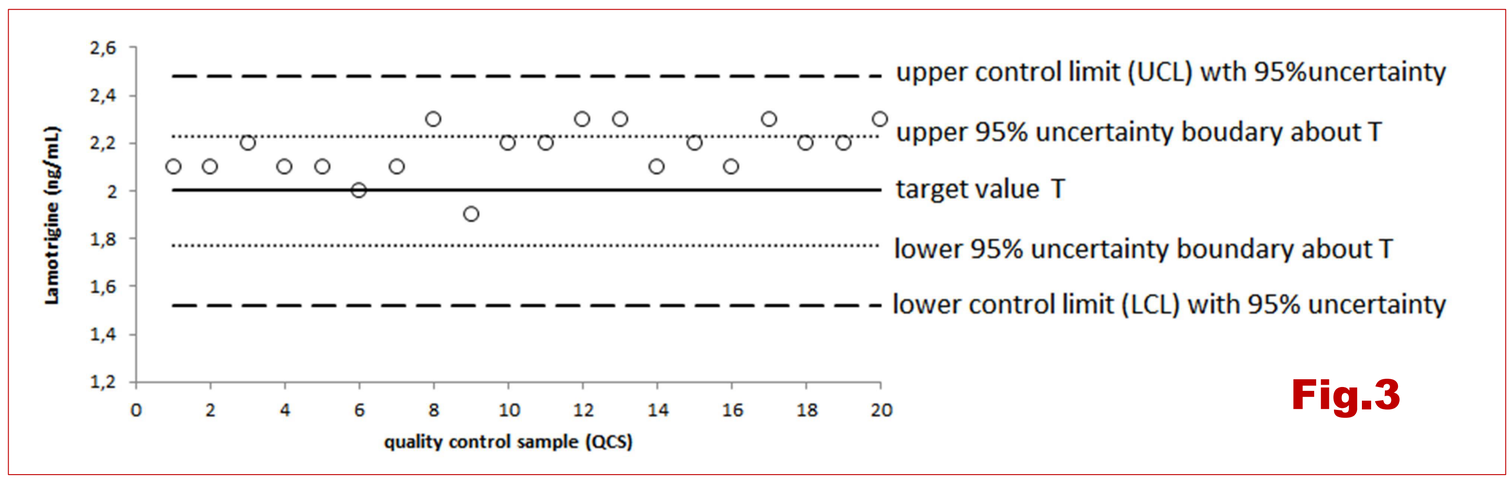


Fig.3

## CONCLUSIONS

Commercially available QCS with lot-to-lot constant nominal value should report also the uncertainty due to batch production tolerance for allowing consistent and effective SCC application.

## References

(1) Patsalos PN, Spencer EP, Berry DJ. Therapeutic Drug Monitoring of Antiepileptic Drugs in Epilepsy: A 2018 Update. Ther Drug Monit. 2018 Oct;40(5):526-548.

(2) (2) Hack PS, ten Caten CS, Effect of Measurement Uncertainty in Control Charts, International Conference on Industrial Engineering and Operations Management 2012, http://www.abepro.org.br/biblioteca/icieom2012_submission_17.p