Letter to the Editor

Mauro Panteghini*

Reply to Westgard et al.: 'Keep your eyes wide … as the present now will later be past'*

https://doi.org/10.1515/cclm-2022-0557
Received June 7, 2022; accepted June 8, 2022;
published online July 4, 2022

Keywords: analytical performance specifications; internal quality control; traceability.

*'*The times they are a-changing', Bob Dylan (1964)*.

To the Editor,

I thank Westgard and co-workers [1] for their interest in our purpose and for giving me the opportunity to explain in more detail and clarify the commented concepts. By the way, it is not the first time that these Authors are stimulating our thinking about the need to apply metrological traceability concepts to the analytical quality control for surveying assay standardization, trying to reconcile the present (or the past?) with the future (or the present?) [2, 3].

The Authors' commentary refers to one aspect of our articulated proposal rethinking the internal quality control (IQC) in the traceability era [4]. It relates to the IQC component I intended to check the alignment of the *in vitro* diagnostics (IVD) measuring systems to the selected higher-order references. Our profession urgently needs to develop a specific strategy that permits to verify in real time the traceability of clinical results [5]. The quoted Clinical and Laboratory Standards Institute (CLSI) guideline has merits, but nothing is reported on how IQC should be designed to contribute to evaluating and monitoring metrological traceability of IVD measuring systems [6]. As a matter of fact, the CLSI C24-Ed4 suggestions use two main premises that are not in line with the correct implementation of metrological traceability in Laboratory Medicine. First, step 1 in the CLSI planning process is (correctly) the definition of the quality required for intended use of a measuring system, but in the form of an allowable total error (TE) that becomes the basis for developing the IQC strategy. I do not want to reiterate here the debate between the TE advocates and those conversely supporting the importance of measurement uncertainty (MU), which requires special attention to the bias component and its correction [7]. I would like just to remember that the common model employed to derive a limit for the allowable TE uses a mathematically incorrect method relying on the sum of mutual exclusive terms [8]. Second, the fundamental principle of CLSI C24-Ed4 guideline is that each laboratory should characterize its own performance, using its experimental mean and SD in calculation of control limits. This make however impossible to establish if the individual measuring system performance is properly unbiased. The example described in Figure 1 of our report clearly showed the high vulnerability of this approach in terms of metrological traceability [4]. Moreover, the statistical dispersion of data obtained by the laboratory (e.g., ±2 SD of the mean value) has no relationship with clinically suitable analytical performance specifications (APS).

Therefore, the ideas that a manufacturer sets the system-specific target values and their acceptability ranges, and that the laboratory should substitute a self-defined allowable SD with a properly derived APS are not erroneous, but integral to the use of IQC for the surveillance of IVD device traceability. Already in 2014, we recommended that IVD manufacturers should provide control materials as a qualified part of the measuring system; these materials, representing the IQC component I, should be designed for daily monitoring of the measuring system alignment, with appropriate target values and acceptability range [5]. This relies on the concept that, if the traceability of the measuring system to higher-order references is granted by the manufacturer, component I materials, which are part of the whole measuring systems, should act as a suitable surrogate of the employed reference to permit routine checking of the correctness of system alignment to such reference [5].

I believe that it is quite reductive to consider our proposal about the criteria for interpreting IQC component I and establishing validation limits as "a simple matter of drawing acceptability limits on a control chart" [1]. Two full columns of our Perspective article were devoted to discussing this issue. We rather stated that "this approach, i.e., checking if the single control value is (or is not) in the

***Corresponding author: Mauro Panteghini**, Research Centre for Metrological Traceability in Laboratory Medicine (CIRME), Università degli Studi di Milano, Milan, Italy, E-mail: mauro.panteghini@unimi.it

Open Access. © 2022 the author(s), published by De Gruyter. This work is licensed under the Creative Commons Attribution 4.0 International License.

acceptable range, if used in isolation is not sensitive and precocious enough to prevent poor quality results on clinical samples. The interpretation of [component I] results by checking their temporal trend without waiting for out-of-control signals is surely more effective." [4]. In this light, I consider the contribution of Westgard and coworkers helpful for further expansion of our proposal, providing that they work is developed by thinking about unbiased results, then replacing TE concept with MU. The next step forward would be therefore to adapt their approach to 0 bias using objectively derived APS for MU [9]. After all, even the Authors recognized that the "tolerance range can be based on the desired APS for MU" [1]. Accordingly, let me conclude by rephrasing in an opposite favourable way the Nobel laureate Robert Allen Zimmerman's words and adapt them as a wish to this reply to Westgard et al.: 'Please come to the new road if you can lend your hand'.

Research funding: None declared.
Author contributions: Single author contribution.
Competing interests: Author states no conflict of interest.
Informed consent: Not applicable.
Ethical approval: Not applicable.

References

1. Westgard JO, Bayat H, Westgard SA. How to evaluate fixed clinical QC limits vs risk-based SQC strategies. Clin Chem Lab Med 2022; 60:e199–201.
2. Panteghini M. Application of traceability concepts to analytical quality control may reconcile total error with uncertainty of measurement. Clin Chem Lab Med 2010;48:7–10.
3. Panteghini M, Sandberg S. Total error vs. measurement uncertainty: the match continues. Clin Chem Lab Med 2016;54:195–6.
4. Braga F, Pasqualetti S, Aloisio E, Panteghini M. The internal quality control in the traceability era. Clin Chem Lab Med 2021; 59:291–300.
5. Braga F, Panteghini M. Verification of in vitro medical diagnostics (IVD) metrological traceability: responsibilities and strategies. Clin Chim Acta 2014;432:55–61.
6. CLSI. Statistical quality control for quantitative measurement procedures: principles and definitions. In: CLSI guideline C24, 4th ed. Wayne, PA: Clinical and Laboratory Standards Institute; 2016.
7. Braga F, Panteghini M. The utility of measurement uncertainty in medical laboratories. Clin Chem Lab Med 2020;58:1407–13.
8. Oosterhuis WP. Gross overestimation of total allowable error based on biological variation. Clin Chem 2011;57:1334–6.
9. Braga F, Panteghini M. Performance specifications for measurement uncertainty of common biochemical measurands according to Milan models. Clin Chem Lab Med 2021;59:1362–8.