





# Comments to the International Council for Standardization in Hematology Guidance for New Lot Verification of Coagulation Reagents, Calibrators, and Controls

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The International Council for Standardization in Hematology (ICSH) recently published a guidance on lot verification of reagents, calibrators, and quality controls in coagulation in this journal.<sup>1</sup> According to the authors, existing guidance from the Clinical and Laboratory Standards Institute (CLSI) and Food and Drug Administration (FDA) regarding lot verification contains no explicit practical guidance on how to perform reagent lot acceptance testing.<sup>2,3</sup> Similarly, standards from the Clinical and Laboratory Improvement Amendments (CLIA) and College of American Pathologists (CAP) as well as ISO15189 formulate requirements, but provide no instructions on how reagent lot acceptance testing should be performed and certainly do not address specific issues for measurands in coagulation.<sup>4-6</sup>

Recent guidance on between-reagent lot variation by a working group of the European Federation of Clinical Chemistry and Laboratory Medicine (EFLM)<sup>7</sup> addresses two important aspects of lot acceptance testing, not addressed by the current ICSH guideline: (1) How to avoid missing cumulative trends, which can occur when every new lot is only compared with the previous/current lot and not (also) to a long-term all-lot anchor and (2) how to distribute the analytical measurement uncertainty budget for overall analytical measurement uncertainty between within-lot and between-lot sources of variation. We believe that these

aspects are critical in the lot verification process and should therefore be taken into consideration. In addition to addressing these important matters, we also highlight other recent publications on lot-to-lot variation.

The cumulative effect of systematic drift in reagent lots over time can lead to an unacceptable difference between results produced using different lots within a certain period. Although CLSI EP26A even in its most recent update neglects to address this issue, already in 2015 a statistical approach and an accompanying spreadsheet calculator were described by Liu et al to address this.<sup>2,8</sup> Other recent literature, including the EFLM working group on accreditation and ISO/CEN standards (EFLM WG-ISO/A) guidance, recommends laboratories not to over-rely on the results of only two consecutive (new and preceding) lots in determining the acceptability of a new lot. Instead, a laboratory should compare the results of a new lot to the average of several previous or other lots.<sup>7-10</sup>

To illustrate these points, consider the scenario involving eight consecutive lots depicted in **Fig. 1**. When judging the second lot (time point A), the laboratory can only compare it to the previous (first) lot. Without information about other lots, the difference between the two lots may be considered unacceptable, and the second lot is rejected. However, as more lots are evaluated, it becomes clear that

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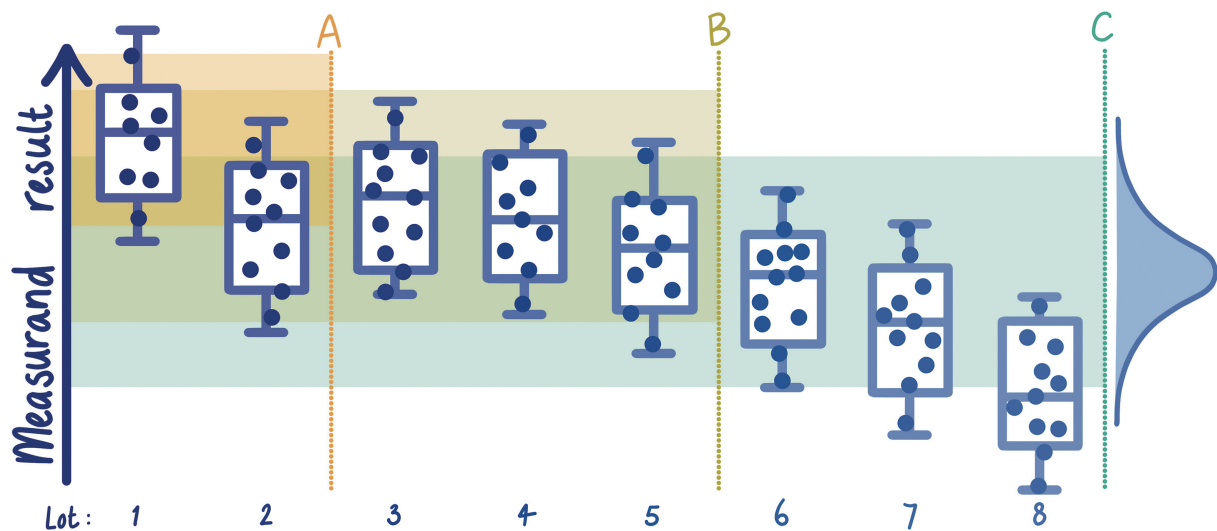
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**Fig. 1** Box plot of eight lots and their distribution depicted as Gaussian curve, with allowable limits to be applied to the medians of new lots indicated as orange (A), beige (B), and green area (C). With the use of consecutive lots, information grows on the contribution of the different lots to the all-lot mean and variation around that mean. At point A, lot 2 seems to be lower compared with lot 1. At time point B it becomes clear that not lot 2, but lot 1 was the atypical lot and at time point C it is clear that the accumulation of small shifts in the same direction since lot 5 ultimately leads to the fact that next to lot 1 also lot 8 has a median outside the 3 SD of the mean of all lots.

it was the first lot, not the second, that was an outlier (and should be rejected, time point B). Additionally, ► **Fig. 1** also depicts how small analytical drifts between consecutive lots (lots 3–8) can be accepted and accumulates to an unacceptable degree over time (time point C).

When introducing a new measurement procedure, a laboratory may lack sufficient historical lot information to guide lot acceptability decision. This knowledge gap can be overcome by using data from (1) the manufacturer, provided as part of the documented metrological traceability, including the between-lot uncertainty, as required by the In Vitro Diagnostics Regulation (IVDR); (2) sharing of data from the (inter)national or regional laboratory community; and/or (3) external quality assessment (EQA) programs that includes lot number information.<sup>9–11</sup> In all these situations it is important that the material used to compare the lots is stable over the period of assessment and commutable between the reagent lots examined. We acknowledge that this can be challenging for some coagulation analytes but still, stable and commutable materials are essential in reagent lot verification. The use of materials that are not commutable between reagent lots can potentially do more harm than good, as described by Stavelin et al for prothrombin time international normalized ratio (INR).<sup>12</sup> Split patient samples, which are commutable by definition, can be used to study lot changes in cases where commutable control materials are unavailable.<sup>12</sup>

With improved manufacturing of both laboratory instruments and reagents, the short-term imprecision (within-reagent lot variation) has decreased over the last decades. This should be considered as progress in the reduction of measurement uncertainty toward required analytical performance specifications. Consequently, between-lot variation has become relatively larger and more noticeable. A significant shift between reagent lots can lead to an errone-

ous impression of a shift in the patient results, which may be misinterpreted as a change in the clinical condition. This risk is higher when the within-reagent lot variation is small and when more results are produced using the same lot.

To manage the between-lot variation and minimize the risk of erroneous result interpretation, the EFLM WG-ISO/A has provided recommendation on the allocation allowable analytical measurement uncertainty for between-reagent lot variation that considers the number of results produced using the same reagent lot.<sup>7</sup> As ISOTS20914:2019 dictates, the bias of a new lot can be corrected, but this correction increases the uncertainty associated with the measurement.<sup>13,14</sup> In cases where the resulting total uncertainty consequentially exceeds the allowable measurement uncertainty, the lot should be rejected.<sup>13,14</sup> The introduction of factors also introduces risk for error and requires frequent reassessment for their persistent need. Moreover, the introduction of factors causes unavoidable local differences between laboratories, which may frustrate harmonization efforts. Therefore, the use of such factors should be limited to situations where the lack of correction would hamper correct medical classification or monitoring of patients and justifies the need to take laboratory responsibility on a “CE-marked” product under IVDR jurisdiction.<sup>15</sup>

As coagulation laboratory tests are also used to manage long-term, steady-state patients with multiple results measured on the same reagent lot, the consequences of long-term drifts and misinterpretation pose realistic risks that ought to be managed in laboratory quality management. This is particularly true in the use of INR for the management of oral anticoagulation therapy.

We hope that our references to other recent guidance on these two important issues addressed in this letter will enhance the understanding of the readers of the ICSH guidelines on managing between-reagent lot variation. Improved

reagent lot change management can aid requesting physician to safely judge patient's steady state without the risk of misinterpretation brought on by short-term shift or long-term cumulative drift.

#### Conflict of Interest

None declared.

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