More on Lot-to-Lot Changes

To the Editor:

Shifts in patient results due to reagent lot changes are a major issue for laboratories, and their investigation is both time-consuming and expensive. In a recent article, Algeciras-Schimnich et al. (1) point out the effect that reagent lot-to-lot changes over time can have on patient results and how these shifts, if large enough, could lead to misdiagnosis and inappropriate treatment. As was the case in this article, on insulin-like growth factor 1, it is often clinicians who alert the laboratory to changes in patient results. We have had similar experiences for a number of analytes, including creatinine. For this analyte, clinicians monitoring renal transplantation patients have asked whether changes as small as from 1.13 mg/dL (100 μmol/L) to 1.24 mg/dL (110 μmol/L) are real or due to shifts in the assay.

In the laboratory, shifts in patient results can be caused by a number of assay system components, but the most likely are reagent lot changes, as described by Algeciras-Schimnich et al. (1), or variations in the assigned values for calibrators (2). In accordance with European Union Directive 98/79/EC, manufacturers should assign values for calibrators via a well-defined traceability chain, but as described recently, there are no agreed criteria for defining allowable limits for the individual steps of the chain (3).

Laboratories experience additional complications with lot changes, because some manufacturers assign values for QC material to specific reagent and/or calibration lots, e.g., Roche Precipath and Precinorm, which can mask any shifts in patient results. Furthermore, we have observed, especially for alkaline phosphatase, shifts in third-party QC material with reagent lot changes that on investigation led to no shift in patient results. For some analytes, monitoring external quality assurance may not always show lot-to-lot shifts to have occurred in the laboratory when one manufacturer’s method dominates the market. The median target value for these analytes will be highly influenced by the predominant method, and its value is likely to be the median value for the lot in use. That may have been the case for the insulin-like growth factor 1 example cited above, because the Mayo Clinic and the University of Virginia laboratories were enrolled in the College of American Pathologists program, in which the Siemens Immulite method was the only method listed in the participation summary. The University of Virginia laboratory was also enrolled in the UK National External Quality Assessment Service program, in which use of the Immulite method accounted for 81 of the 90 participants (D.E. Bruns, personal communications, August 17 and 19, 2013; A. Algeciras-Schimnich, personal communication, August 19, 2013).

As Algeciras-Schimnich et al. (1) pointed out, it is not practical for every laboratory to do a full evaluation of every lot change, whether reagent or calibrator change. They also question whether manufacturers’ criteria are sufficiently stringent. We suggest that currently they probably are not, despite the regulatory requirements (2). Even for albumin, a very commonly measured analyte with a well-documented methodology, the reference measurement system (and the associated uncertainty) is probably not adequate to guarantee the accuracy required for the clinical usefulness of this analyte (4).

One suggestion to address the problem is to enable centralized monitoring of patient results with coordination by the manufacturer, especially for low-volume tests. That would require agreement for laboratories to release their de-identified results. This approach may happen eventually, but in the meantime, laboratories must develop procedures to recognize and evaluate lot-to-lot changes. Monitoring the mean of the healthy population also provides a means of assessing lot-related changes, but such monitoring is by its very nature a retrospective assessment.

It is not that laboratories are seeing more variation in different lots, but as assays and equipment become more precise and clinicians become more demanding, laboratories are tightening their acceptability criteria. With personalized medicine and wellness testing becoming more prevalent, laboratories and manufacturers will need to work together to ensure that the results they produce are both accurate and meaningful. Whichever way the problem is tackled in the future, lot-to-lot changes are going to be a major issue confronting all laboratories.

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