COLLEGE of AMERICAN PATHOLOGISTS

CLIAC November 2024

CAP Statement on Proficiency Testing: Determination of Clinically Relevant Range of Values

The College of American Pathologists (CAP) appreciates the opportunity to provide written comments to the Clinical Laboratory Improvement Advisory Committee (CLIAC) regarding the terms “clinically relevant values” and “full range of values” as they relate to proficiency testing (PT) in the CLIA regulations. As the world’s largest organization of board-certified pathologists and leading provider of laboratory accreditation and proficiency testing programs, the CAP serves patients, pathologists, and the public by fostering and advocating excellence in the practice of pathology and laboratory medicine worldwide.

As stated in the Code of Federal Regulations, the terminology used is “clinically relevant range[1]”, “full range of values[2]” and “full range of interpretation that would be expected in patient specimens[3]”. As written, the variation between these terms invites confusion. However, we urge CLIAC engage in robust discussion to understand the needs and considerations of laboratory stakeholders, and to share a clear vision of the agencies’ intent regarding revising CLIA’s language around range of values.

While the CAP supports increased clarity in the range of values for PT, the details become much more complicated. Complications to consider include potential manufacturing limitations, clinical utility of the test, assay harmonization status, lack of globally accepted reference intervals, cost, and impact on PT performance. Otherwise, the PT challenge risks inadvertently becoming a problematic exercise with limited value to laboratory participants.

About 500 physicians and doctoral scientists with expertise in pathology and laboratory medicine serve on the 29-discipline specific scientific committees within the CAP. In their advisory role, our members oversee, review anonymous PT performance data, write scientific discussions when applicable to educate laboratory personnel, and set specifications and targets for the CAP PT programs. When writing PT specifications, consideration is given based upon clinically relevant ranges and values, availability of appropriate materials our expert members feel are most important for ensuring appropriate high quality patient care, and compliance with the regulatory requirements listed in Subpart I.

Occasionally, for certain analytes, it is difficult to offer a challenge at the lowest end of the reference range due to manufacturing limitations. Additionally, many routine analytes have negligible clinical significance at low concentrations (e.g., aspartate aminotransferase). Our committee members, most of

[1] Subpart I Proficiency Testing Programs for Nonwaived Testing
[2] § 493.937 Toxicology and § 493.941 Hematology
[3] § 493.959 Immunohematology

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whom serve as laboratory directors, set specifications for PT samples that would be expected in clinical specimens and are keenly aware where medical decisions are made. It is also worth mentioning that it becomes exceedingly difficult to offer an analyte at the low concentration when the regulations do not allow fixed limits with fixed percentage units, so PT providers could use the acceptance limit, whichever is greater/more tolerant.

A couple of examples with manufacturing limitations, or lack of clinical utility:

- Offering artificially low prothrombin time (PT) or activated partial thromboplastin time (aPTT). The CAP Hemostasis and Thrombosis Committee deems such low levels as having no clinical utility in challenging the lower end of the PT or in aPTT reference intervals, and such low values are mostly caused by laboratory artifacts. From manufacturing standpoint, it is challenging to create a sample with abnormally short PT or aPTT time (in seconds), as it would be of concern that manipulation would make the proficiency testing sample unsuitable and potentially ungradable, as experienced few years back in the CAP Coagulation PT Program. Manipulations of plasma to achieve such low levels is also very costly with no added value to participants. Additionally, in the context of lack of assay harmonization or globally accepted reference intervals, proficiency testing samples that challenge the low end of the range for one assay may not recover similarly across all assays. Such differences in PT performance are likely due to sample variation secondary to the manufacturing process rather than a reflection of meaningful laboratory testing performance differences, and as such, it becomes burdensome for laboratories as they are required to perform alternative performance assessment when a PT provider is unable to formally grade/evaluate a challenge.
- Another example that has presented manufacturing limitation is to offer T3-Uptake on the low end of the reference range. Even at the endogenous levels, addition of buffer, pH solutions, background analytes increase the T3-Uptake values, rendering the challenge as not meeting the regulatory requirement. Of the fifteen challenges offered throughout the year, every effort is made by the CAP to challenge the laboratories in covering the clinically relevant range of the analyte values expected in patient specimens.

We hope that broader, robust discussions with key stakeholders and PT providers will be held prior to advancing proposed regulatory revisions on this important issue. The CAP stands ready to contribute our scientific knowledge and real-world experience to such discussions.

Once again thank you the time to discuss the CAP's concerns and recommendations and we welcome the opportunity for further dialogue. Please contact Andrew Northup at anorthu@cap.org or 202.297.3726.

Closing,

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