AACC Forum; The road to harmonization: regulatory considerations for recalibrating IVD devices.

June 26, 2013.

Summary of Discussion

The purpose of the Forum was to identify and address regulatory concerns of the IVD industry regarding changing the calibration traceability of existing IVD devices to align with national or international consensus recommendations from clinical and/or laboratory groups to improve the quality of clinical decisions based on laboratory test results. It was agreed that it is desirable to have an expeditious process for such calibration adjustments that is consistent with patient safety considerations.

The Forum was organized by AACC as part of its harmonization initiative in collaboration with AdvaMedDx and the FDA.

The attachments provide the presentations made by each speaker to set the stage for the discussion sessions and the list of participants.

The following statements summarize the discussion which represents the clinical laboratory community's current understanding of the regulatory process as it applies in particular to calibration adjustments and identifies items for follow up actions.

1. It is generally preferable to have calibration traceable to an accepted reference measurement procedure and/or a commutable reference material as a mechanism to promote harmonization among results from different IVD devices.

2. It is acceptable to use calculations, based on the relationship between a current and an adjusted calibration traceability scheme, to update IVD device parameters such as reference intervals or other parameters that will not be affected other than proportional numeric thresholds when calibration is adjusted. Manufacturers are encouraged to contact the FDA for advice regarding the need for a submission when the calibration traceability is updated.

3. The FDA has available a triage program to simplify the 510(k) process for high quality submissions. In addition, the Special 510(k)

process is also available for many device modifications; this process relies primarily on a company's internal quality system documentation for an update.

4. The FDA encourages manufacturers to contact them in advance of a submission through their pre-Submission review process to discuss what is needed and to agree if a simpler process is applicable for a planned change in calibration traceability. The amount of documentation depends on the changes included in the submission, the risk to patient safety, and other factors that will be different for different measurement procedures. In a submission, it is helpful to clearly explain that the submission is to support a calibration adjustment to conform to consensus professional recommendations to avoid any misunderstandings during the review.

5. The FDA reported that there are inconsistencies in submissions from different manufacturers that could be minimized and lead to simpler submissions by better communication from manufacturers in advance of a submission. Manufacturers can access previous FDA submission reviews, including those from other manufacturers, as examples to follow for similar submissions such as for adjusting calibration traceability.

6. The FDA addresses consistency among reviewers by internal training and by providing new reviewers with mentoring assistance. All impactful decisions undergo management review before finalizing a response to a submission. The submitter can assist with consistency by alerting the FDA to any previous communications regarding a given submission or resubmission. Like any communication, those from the FDA can be misinterpreted; the FDA recommends to ask for clarification if an interpretation does not seem to make sense.

7. A question was raised if the FDA can endorse, for example, reference measurement procedures listed by the JCTLM as preferred for calibration traceability. Such a process would be addressed within the FDA as a guidance which is a time consuming process that is challenging given the available resources. It would be helpful to have a prioritization process that may allow the FDA to address a select few high-priority measurands. The new International

Consortium for Harmonization of Clinical Laboratory Results will provide such a prioritization process that may contribute to such guidance.

8. Manufacturers can collaborate to address one or more measurands by developing a process for the data needed for a calibration adjustment (or other common parameters) that a group of manufacturers and the FDA agree to in advance. Such an approach can provide consistency, coordinate submissions to the FDA, alert the FDA to when such coordinated submissions will occur, and simplify the submission and review process. Such an approach would be particularly applicable to high priority measurands for which there is a consensus in the clinical laboratory community for changes that are needed. Cystatin C was mentioned as a potential test for manufacturers to explore whether working together would streamline the regulatory approval process. AdvaMedDx may be able to assist with coordination among manufacturers.

9. Complex new standardization activities should be communicated to the FDA as early in the process as possible (e.g., through the pre-Submission review process) and work with the FDA to agree on a plan that will be successful when manufacturers submit for review.

10. Clinical studies data is the most expensive component of a submission. When a change in performance can be explained by a calibration adjustment, it may not be necessary to include new clinical studies in 510(k) submissions. The FDA should be consulted in advance for assistance in determining data requirements. For PMA (Class III) submissions, clinical data may be required but there are relatively few diagnostic tests that require PMA submissions, especially when calibration adjustment is the primary change to be implemented.

11. Education is needed to inform physicians and laboratory staff on the need to introduce standardized procedures to include how the change will improve patient care and how the standardized results should be interpreted. Medicine evolves over time and physicians are accustomed to adjusting their decisions based on improvements in laboratory testing. Laboratory professionals should be encouraged to

interact directly with clinician colleagues in the proper interpretation of laboratory test results.

12. The laboratory community should revisit the number of significant figures reported to avoid giving a false impression of the degree of uncertainty in a given laboratory result.

13. Changes in laboratory values for patient samples may be associated with renewal lots (or batches) of reference materials. Such changes typically do not initiate a submission to the FDA but do represent inconsistency in results and may affect interpretive criteria. The laboratory community should develop guidelines for acceptable practices when renewing lots (or batches) of reference materials.