Dr. Rifai and coauthors seem to have misunderstood the guidance proffered by the US Food and Drug Administration (FDA)1 and the laboratory safety tip addressing the issue of matching claims with performance data for C-reactive protein (CRP) assays. The FDA believes that different claims for CRP require very different data sets and different performance criteria to support differing intended uses.

FDA premarket guidance proposals are written to benefit companies and FDA reviewers regarding recommendations for studies that support premarket submissions for medical devices in the United States. They are not meant to be clinical practice guidelines; however, FDA guidelines are meant to be based on sound science, committed to truth in labeling, and intended to help to ensure the safety and effectiveness of medical devices for the promotion of public health.

The driving force behind FDA premarket assay reviews is based on the indications for use of a given assay. For regulatory purposes, the distinction between CRP assays, high-sensitivity (hs)CRP assays, and cardiac (c)CRP assays lies with the Indications for Use. In the Guidance for Industry and FDA Staff: Criteria for Assessment of C-Reactive Protein (CRP), High Sensitivity C-Reactive Protein (hsCRP), and Cardiac C-Reactive Protein (cCRP) Assays (1), the discussion on indications for use can be found in Section 5: Types of CRP Assays. This section states that, although all CRP assays start with the same basic indications for use (i.e., general evaluation of infection, tissue injury, and inflammatory disorders), hsCRP assays and cCRP assays have additional claims.

hsCRP assays are intended for more sensitive detection of inflammatory states, whereas cCRP assays are intended for use in cardiovascular risk assessment. FDA data requirements differ for each of these 2 intended uses. The regulatory distinctions in both claims and data requirements have been established to assist manufacturers, FDA staff, and laboratory users to understand the different types of performance data gathered to support a particular assay.

The hsCRP assay indication is based on data demonstrating the ability to analytically measure a lower CRP concentration than the traditional or older CRP assays. When compared with traditional assays, this increased analytical reliability may be useful in the clinical investigation of conditions associated with inflammation. This

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Counterpoint Food and Drug Administration Guidance for C-Reactive Protein Assays: Matching Claims with Performance Data

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1 Nonstandard abbreviations: FDA, US Food and Drug Administration; CRP, C-reactive protein; hsCRP, high-sensitivity CRP; and cCRP, cardiac CRP.
improved measure of performance does make the assay a potential candidate for use as an aid in assessment of cardiovascular risk. However, because the hsCRP does not carry a specific claim for cardiovascular risk, the FDA does not require additional clinical or analytical data to link these assays to cardiac endpoints. If these are used in cardiovascular risk assessment, it is suggested that results be interpreted with caution because of the uncertain association of test results with the clinical endpoints of interest. Manufacturers may provide physicians a well-rounded discussion of published peer-reviewed studies. However, to make a specific claim for appraisal of cardiovascular risk, the FDA would require clinical data demonstrating the strength of association or analytical data that would allow an assay to bridge, in a strong and unequivocal manner, to clinical studies that demonstrate this association.

The cCRP assay indication for use, in contrast to the hsCRP, does carry a specific claim for cardiovascular risk. As a result, the FDA does require additional clinical and/or analytical data to demonstrate an association of the assay with cardiovascular endpoints. The elucidation of these differences is a major objective of the new guidance.

Thus, although the expected performance criteria in the new guidance are similar for hsCRP and cCRP assays, they are not, as Rifai and coauthors suggest, identical. Although Rifai et al. are correct that many hsCRP assays have been developed using standardized materials, they are not correct to assume that, as a result, all assays are equal in performance. New criteria for both hsCRP and cCRP have evolved over time, and the hsCRP assays themselves have been standardized by use of incongruent techniques; they are not commutable, and they have not been linked in a predictable manner to any clinical endpoints. Review of both proficiency testing results and recent publications in the literature clearly suggest that, when different assays are used, single-sample hsCRP results vary significantly, emphasizing a need for additional standardization (2–7). By our interpretation, the CDC standardization study (8) referenced by Rifai et al. further highlights the need for standardization in this field beyond simple traceability to Certified Reference Material 470. The assays studied exhibited high variability despite all being ultimately traceable to the same reference material. The FDA guidance provides information on how companies may address this standardization problem and how to gather either clinical or analytical data to demonstrate that these assays can be used as safe and effective tools in identifying cardiovascular risk.

The FDA CRP guidance is intended to facilitate the regulation of CRP assays for various indications. To achieve this end, and in an effort to create a useful and thoughtful guidance document, we will fully consider all comments that we receive. Written comments and suggestions for the guidance document may be submitted at any time for Agency consideration to the Division of Dockets Management, Food and Drug Administration, 5630 Fishers Lane, Room 1061 (HFA-305), Rockville, MD 20852. When submitting comments, please refer to the exact title of the guidance document. For questions regarding the document, contact James V. Callaghan by phone at 240-276-0443, or by e-mail at james.callaghan@fda.hhs.gov.

Additional information may also be found on our webpage, under the category “Tips for Clinicians and Laboratorians”. See “C-Reactive Protein (CRP): The Differences Amongst Various Assays” (posted March 15, 2006) at http://www.fda.gov/cdrh/oivd/tips/crp.html.

References

1. US Food and Drug Administration. Guidance for industry and FDA staff: criteria for assessment of C-reactive protein (CRP), high sensitivity C-reactive protein (hsCRP), and cardiac C-reactive protein (cCRP) assays. http://www.fda.gov/cdrh/oivd/guidance/1246.html.


