



Advancing
Clinical Laboratory
Science Worldwide

May 5, 2003

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

Docket# 03D-0044

Dear Sir/Madam:

The American Association for Clinical Chemistry (AACC) welcomes the opportunity to comment on the Food and Drug Administration's (FDA's) draft guidance entitled, "Statistical Guidance on Reporting Results from Studies Evaluating Diagnostic Tests; Draft Guidance for Industry and FDA Reviewers," which describes statistically appropriate practices for reporting results from different types of studies evaluating diagnostic tests. Our specific comments follow.

AACC supports the FDA's efforts to promote statistically appropriate practices supporting the performance of new diagnostic tests and to create uniform definitions of clinical sensitivity and clinical specificity. We further agree that manufacturers submitting premarket approval (PMA) applications and premarket notifications [510(k)s] should use consistent, appropriate language when describing the performance of diagnostic tests.

In the guidance, the agency lists four different comparative procedures that a manufacturer could use to evaluate a new diagnostic test—the "perfect standard" or three alternative approaches. The agency emphasizes that manufacturers should use or develop, whenever possible, a "perfect standard" for evaluating new diagnostic tests. AACC agrees with this approach. Although we recognize that comparisons to the clinical status are sometimes difficult or impractical, the "perfect standard" should always be the measure to which other comparisons are subordinate. We do recommend, however, that the agency further elaborate on the criteria for making a diagnosis (disease presence or absence) and how they should be documented as part of the clinical sensitivity and specificity studies.

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FDA
May 5, 2003
Page Two

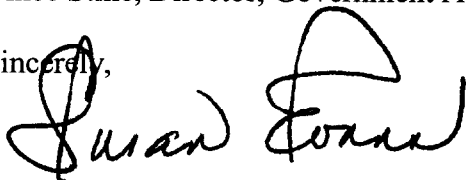
AACC also recommends that the agency include language that limits circumstances under which a manufacturer could compare a new test to an existing test that *employs the same analytical methodology*. When such circumstances do exist, additional measures should be required that preclude bias and analytical non-specificity. Such a requirement should be included as an additional paragraph at the end of the "General Reporting Recommendations" section [top of page 6].

We also want to bring to your attention a document prepared by Medicare Coverage Advisory Committee (MCAC), "Recommendations for Evaluating Effectiveness," which addresses many of the same issues as the FDA guidance, such as study design and interpretation of results, as well as emphasizes evidence-based studies as the preferred type of evaluation process. We encourage the FDA to review this document, located at <http://www.cms.hhs.gov/mcac/8b1-i19.asp>, and incorporate or cite sections, where appropriate. (While we recognize that the Draft Guidance is intended for qualitative tests only, we believe that many of the fundamentals of sensitivity, specificity, and study design apply equally to both qualitative and quantitative tests.)

Finally, we urge the agency to include additional examples (see Addendum); in both the text of the document, and the Appendix, to assist manufacturers, clinical researchers, and FDA reviewers, among others to more clearly understand the purpose of the document.

By way of background, AACC is the principal association of professional laboratory scientists--including MDs, PhDs and medical technologists. AACC's members develop and use chemical concepts, procedures, techniques and instrumentation in health-related investigations and work in hospitals, independent laboratories and the diagnostics industry nationwide. The AACC provides national leadership in advancing the practice and profession of clinical laboratory science and its application to health care. If you have any questions or we may be of any assistance, please call me at (408) 395-0807 or Vince Stine, Director, Government Affairs, at (202) 835-8721.

Sincerely,

A handwritten signature in black ink, appearing to read "Susan Evans". The signature is written in a cursive, flowing style with a large initial "S" and "E".

Susan Evans, PhD
President

Addendum

Specific Changes and Examples

We believe, as stated earlier, that the “perfect standard” should always be comparison to the clinical status of the patient, and we recommend that this be emphasized through the use of examples.

(Page Two, Introduction, Second paragraph, Fourth line)

When the comparative procedure ~~is generally accepted~~ has been validated as an indicator of true clinical status by the clinical community and ~~is regarded as having~~ has been shown to have negligible risk . . .

(Page Four, General Statistical Guidance for Evaluating a New Diagnostic Test, If a perfect standard is available, use it)

From a purely statistical perspective, the best approach is to compare the new test to the patients’ clinical status ~~or to a perfect standard using specimens, drawing~~ from patients who are representative of the intended use or population. In this situation, sensitivity and specificity have meaning and you can easily calculate the estimates (as described in the numerical example in the Appendix). ~~The Appendix describes a numerical example.~~

For example, a new diagnostic marker of myocardial injury is best compared is to the patients’ clinical status, not to the presence or absence of another diagnostic marker.

(Page Four, General Statistical Guidance for Evaluating a New Diagnostic Test, If a perfect standard is available but impractical, use it to the extent possible, First Paragraph)

After the last sentence in the first paragraph, insert:

For example, a diagnostic test for male fertility is best compared, for sensitivity purposes, to observed fertility over a defined followup period. Alternative approaches must be used for comparison of specificity results, but to the extent that clinical status, the gold standard, can be used, it should be used.

(Page Four, General Statistical Guidance for Evaluating a New Diagnostic Test, If a perfect standard is not available, consider constructing one)

At the end of the paragraph, please insert:

For example, a urine drug test intended to detect illicit drug use would ideally compare the drug amount, drug purity, and timing of use to the urine test result. Designing such a test for illicit drugs would likely violate ethical (and legal) standards, and therefore comparison to an existing standard is necessary. Such a comparative test should

incorporate as accurately as possible the range of metabolites found in human urine, and not rely on urine “spiked” with parent drug only. However, when the urine drug test is intended to detect legal drugs, studies can be designed which collect specimens from patients for whom such drugs are prescribed, and the test result compared to the patients’ clinical status.