A Scorecard Doesn't Help When the Players Keep Changing Shirts

To the Editor:

Killingsworth describes two recent regulatory initiatives by the US Food and Drug Administration (FDA) and urges the clinical laboratory community to lobby against them (1). Although I agree with many of his points, I suggest a different perspective.

In late summer of 1992, the FDA issued a "Draft Guideline for Compliance" to manufacturers of unapproved test kits being sold "For Research Use Only" in the US, yet being widely used for the diagnosis and monitoring of patients. Many of these tests are for the newer tumor markers and are considered Class III Medical Devices, which require a long and expensive premarket approval process overseen by the FDA's Center for Devices and Radiological Health (CDRH) before they can be used legally in a clinical laboratory. The FDA's jurisdiction here is generally not questioned, although the agency seemed to look the other way for several years, during which time the tests in question gained acceptance among users. The medical community purchased and offered the kits and used the results with little apparent regard for their unapproved status.

If the draft document is enforced unchanged, the FDA will come down hard on those manufacturers of unapproved test kits. Also, some of the same reagents incorporated into stains for histochemistry or flow cytometry will be targeted for sanctions unless submitted for approval. Included among the analytes threatened with sanctions are a few that are Class II Medical Devices (and thus require only a 510(k) clearance before clinical use, in general a much shorter and less expensive process), e.g., lutetianizing hormone and human chorionic gonadotropin. The implication is that when the reagents include monoclonal antibodies and/or the analyte is being used as a tumor marker, the test kit falls into a different regulatory category. Now there is a monster can of worms.

A single paragraph of the compliance document, quoted in full by Killingsworth, has erupted into the "home brew" controversy. As a potential piece of rulemaking, the paragraph is poorly written, unclear, out of context, and probably unenforceable. It certainly should disappear in its entirety, and one can only hope and lobby to make that happen. In some early, unofficial follow-up statements, some sources at the FDA have indicated that the paragraph may not remain as written. The FDA needs to be encouraged in that direction. There is overlap with the Clinical Laboratory Improvement Act (CLIA) quality-control (QC) regulations, as Killingsworth indicates, and, in subpart K of the regulations, CLIA outlines the design of appropriate method evaluation and QC programs for modified or in-house tests.

Urinary testing for the human immunodeficiency virus (HIV), the specific example that Killingsworth uses of a threat to laboratory research and development under the "home brew" initiative, actually represents a different, and probably unrelated, FDA action. In the summer of 1991, the FDA ordered laboratories to stop testing urine with kits licensed for testing serum for antibodies to HIV. The key word here is "licensed." The majority of tests for antibodies to HIV, hepatitis B and C markers, and several other analytes are used not by clinical laboratories, but by the blood-banking community to screen the blood supply. These tests are regulated by a separate section of the FDA, the Center for Biologics Evaluation and Research (CBER). Blood banks themselves, including their testing functions, are regulated by the FDA, not by the Health Care Financing Administration, although agreement has been reached between the two agencies that FDA will regulate blood bank laboratories with CLIA criteria. Tests falling into CBER's jurisdiction are licensed, rather than approved, and the license process, unlike the premarket approval and 510(k) processes, specifically requires that the test be used only according to the manufacturer's directions. Further, manufacturers of licensed test kits are required to submit samples of every lot of kits to the FDA for testing prior to release of that lot for sale, another major difference from CDRH-regulated kits. "Off-label" usage of these tests has never been allowed, a fact that may have escaped many clinical laboratories. The blood banks accept and support this approach to testing, because the fact that they use test kits exactly as the manufacturers and the regulations require should not only ensure maximum consistency of test results, but also protect them in legal situations. Thus, they work with the FDA and use its authorizations as a shield.

Is the FDA a metastasizing organism to fight against, or a filter to assure at least a minimum quality of the test kits that we use? Contrary to the old expression, you probably can have it both ways, but that costs time, money, energy, and lots of ink.

Reference

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Conjugated, but Not Unconjugated, Bilirubin Negatively Interferes in Hitachi 747 Assay of Inorganic Phosphorus

To the Editor:

The most common assays of inorganic phosphorus (P) in serum or plasma are the phosphomolybdate methods: P1 complexes with ammonium molybdate in strong acid, resulting in a complex that can be quantified directly by measuring absorption at 340 nm; alternatively, the complex can be reduced to form a blue complex of unknown structure with a maximum absorption at 680 nm. Our laboratory measures P, both ways—by direct measurement at 340 nm (Hitachi 747; Boehringer Mannheim, Indianapolis, IN) and at 680 nm after reduction (Ektachem E700; Eastman Kodak, Rochester, NY).

During the first 2 months of routine operation with the 747, we noted that many icteric samples produced P1 results 4–10 mg/L lower than those produced by the E700. However, we found no evidence for an interference on either method when samples were supplemented with a bilirubin standard (Instrumantion Laboratory, Lexington, MA). Furthermore, the manufacturers' documentation states that both of these P1 methods are free from bilirubin interference. All icteric samples that produced discrepant P1 contained