Blood Products Advisory Committee Meeting, March 18, 2004:

Topic: Supplemental Testing for HIV and HCV

Issue

FDA seeks the opinion of the Committee on the relative performance of different types of supplemental assay for Human Immunodeficiency Virus (HIV) and Hepatitis C Virus (HCV) to confirm a repeatedly reactive enzyme immunoassay (EIA) screening test result in a blood donor

Background

This discussion is being initiated because of two CDC MMWR communications about diagnostic testing for HCV infection in clinical laboratories (1)(2). The articles describe, in detail, diagnostic testing algorithms for hepatitis C involving the use of anti-HCV ELISA screening assays, the more specific anti-HCV recombinant immunoblot assay (RIBA) and HCV RNA NAT assays. FDA wishes to consider the scientific merits of different approaches to confirmation of screening test results for HCV and HIV as they might be applied in the setting of donor screening, as opposed to medical diagnostic testing. In particular, we would like the Committee to examine the relative advantages and disadvantages of supplemental testing for HIV using the Western blot, nucleic acid test (NAT), and a second EIA; and of supplemental testing for HCV using RIBA and NAT. The Committee also will be asked to consider the merits for use of a high signal-to-cutoff (s/co) ratio in the screening EIA to obviate additional testing.

In the 1998 MMWR article, CDC recommended that a person should only be considered to have serologic evidence of HCV infection (be positive for anti-HCV), after an anti-HCV screening-test-reactive result has been verified by a more specific, supplemental, serologic test, such as RIBA, or a nucleic acid test (NAT). In the later 2003 MMWR article, this principle of retesting screening assay reactive samples using a more specific supplemental assay was reiterated and emphasized.

However, an option was provided for reporting a final positive anti-HCV test result, on the basis of a screening test reactive result with a clearly defined high signal s/co ratio, without supplemental RIBA testing. Thus, if the anti-HCV screening test s/co ratio is higher than the s/co value for the EIA test for which it is known that $\geq$ 95% of repeatedly reactive samples would be positive on a RIBA supplemental test, a positive anti-HCV result can be reported without RIBA supplemental testing. (Supplemental testing is recommended for all repeat reactive samples with lower s/co ratios.)

It is important to note and emphasize that the MMWR article mentioned that this option is to be used only in a clinical laboratory, diagnostic setting. A footnote states that the CDC recommendations are not intended to be used for blood, plasma, organ, tissue, or other donor screening or notification as provided for under FDA guidance or applicable

regulations, and that they are not intended to change the manufacturer's labeling for performing a specific test.

According to 21 CFR 610.40, a blood donation that is reactive must be tested by an additional, more specific supplemental test, if such a test is available and if it has been approved for such use by FDA. The reasons for these differences between the CDC's 2003 MMWR clinical laboratory testing recommendations for detection of hepatitis C infection and FDA's donor testing requirements are discussed below.

Reasons for the Option of Using High Signal to Cutoff Ratios in Hepatitis C Diagnosis in Clinical Laboratory Settings

While donor testing is regulated in regard to additional, more specific supplemental testing, clinical laboratory diagnostic testing, which is a part of the practice of medicine, is not regulated in this way. More specific testing of all screening test reactive samples is always highly desirable, because verifying presence of anti-HCV minimizes unnecessary medical visits and psychological harm for persons who test false positive by screening assays and ensures accurate counseling, medical referral and evaluation. However, clinical testing laboratories are not required to perform supplemental testing, and many do not do so, because of its expense, the lack of routine reimbursement for supplemental testing, and a lack of understanding of the limitations and interpretation of screening test results. Therefore, the less costly method of using clearly defined high s/co ratios, without using supplemental tests, but with an accompanying clear and comprehensive message to the physician, became a recommended option. (Please see the 2003 MMWR article).

Reasons for the Requirement of Supplemental Testing for Reactive HIV and HCV Screening Tests in the Blood Donor Setting

Supplemental testing is required to be performed on donors who test repeatedly reactive on an anti-HIV or anti-HCV screening test, and who are deferred from donating, because providing donors with accurate information about their communicable disease status and deferral as soon as possible helps to ensure a healthy donor population. Moreover, blood and plasma establishments also can use information from supplemental testing to evaluate the donor for possible reentry into the donor pool. Requalification of donors contributes to blood availability, which also is a public health concern. Therefore, FDA believes that mandatory supplemental testing of blood donations has a direct impact on blood safety in preventing communicable disease transmission and on blood availability.

Supplemental Testing for HCV in the Blood Donor Setting

The current testing algorithm for anti-HCV repeat reactive samples requires using RIBA to confirm test results. Data will be presented at the meeting comparing the different strategies, including NAT, to evaluate whether they would be applicable to testing of blood donors.

Supplemental Testing for HIV in the Blood Donor Setting

The current testing algorithm for anti-HIV repeat reactive samples requires using a western blot or IFA followed, in cases of an indeterminate result, by an HIV-2 EIA to confirm test results. An alternate testing algorithm that uses a second (different manufacturer's) EIA, to further define which specimens would be tested by a supplemental test, is being evaluated in the donor setting. Data will be presented at the meeting comparing the different strategies, including NAT, to evaluate whether they would be applicable to testing of blood donors.

Discussion Objectives

FDA would like the Committee to discuss the scientific merit and public health benefit of additional, supplemental, testing in a blood donor setting. More specifically, we would like the Committee to discuss the relative performance characteristics of various supplemental testing strategies for HIV and HCV, including positive predictive value, and comment on the advantages and disadvantages of the different approaches. The Committee will be asked to compare the use of additional tests such as Western blot, NAT, or a second EIA for HIV, and of using RIBA, NAT, or a high s/co ratio for HCV as predictive of the presence of HIV or HCV infection in the donor.

Questions for the Committee

1. Please comment on the relative performance of:
   (i) RIBA versus HCV NAT
   (ii) RIBA versus signal-to-cutoff ratio in the screening test for anti-HCV

   to confirm a reactive screening test result in the blood donor setting. What are the scientific advantages and disadvantages of these different approaches?

2. Please comment on the relative performance of:
   (i) Western Blot versus HIV NAT
   (ii) Western Blot versus a second EIA for anti-HIV

   to confirm a repeatedly reactive screening test result in the blood donor setting. What are the scientific advantages and disadvantages of these different approaches?

References

1. CDC. Recommendations for prevention and control of hepatitis C virus (HCV) infection and HCV-related chronic disease. MMWR 1998;47(No. RR-19):1-33.

2. CDC. Guidelines for Laboratory Testing and Result Reporting of Antibody to Hepatitis C Virus. MMWR 2003;52(No. RR-3):1-16.