

Blood Products Advisory Committee Meeting
March 14-15, 2002

FDA's Current Thinking on Hepatitis A Virus (HAV) NAT for Blood and Plasma

Issue:

FDA seeks to clarify the circumstances under which the Agency would regard NAT testing for hepatitis A to be "in-process" testing, medical diagnostic testing and/or donor screening.

Background

Consistent with the advice of BPAC (held in June 2000), FDA has allowed the testing of plasma pools for HAV NAT as "in-process" tests to ensure the quality of plasma for further manufacture. Test results were used to reject reactive units, but donors were not notified or deferred. BPAC did not recommend resolving the reactive manufacturing pool to the individual donor. FDA will review these NAT methods as analytical procedures with respect to sensitivity, specificity and reproducibility under license supplements for the manufactured products, and in the absence of "free-standing" approvals for the NAT tests per se.

FDA has become aware that Source Plasma fractionators have been performing HAV pool testing and resolving reactive to individual donors. FDA is also aware that Whole Blood industry would like to implement similar HAV NAT screening as those by Source Plasma fractionators. It has been proposed that such testing should be regarded by FDA as "in-process" testing on recovered plasma, and not as donor screening. At least initially, reactive minipools would not be resolved to identify individual reactive donors. Additionally, it has been stated that pre-release testing and labeling is not feasible for blood components, for lack of an appropriate technology infrastructure. As proposed, test kit manufacturers may provide their systems and reagents for such testing. The validation of these test methods would be reviewed under the license supplement mechanism submitted by fractionators.

Hepatitis A, one of the most frequently reported vaccine-preventable diseases in the United States, is caused by the hepatitis A virus (HAV), a small RNA virus classified as a picornavirus. After an incubation period (from contact to symptoms) of 15-50 days, HAV infection can induce acute hepatitis in humans. Viremia occurs soon after infection and persists through the period of liver enzyme elevation. Among older children and adults, infection is usually symptomatic, with jaundice occurring in greater than 70% of patients. Signs and symptoms usually last less than 2 months, although 10-15% of symptomatic persons have prolonged or relapsing disease lasting up to 6 months.

Post-exposure prophylaxis with immune globulin (IG) can prevent or lessen hepatitis A symptoms. Immune globulin, intra-muscular (IGIM) provides protection against hepatitis A through passive transfer of antibody. The concentrations of anti-HAV

achieved following administration of IGIM are below the level of detection of commercially available diagnostic tests. Administration of IGIM within 2 weeks following an exposure to HAV is greater than 85% effective in preventing hepatitis A. When IGIM is administered later in the incubation period, it only attenuates the clinical expression of HAV infection.

The HAV seroprevalence in the US is about 30% and in the developing world reaches levels higher than 95%. HAV is transmitted through the fecal-oral route by either person-to-person contact or ingestion of contaminated food or water. On rare occasions, HAV infection has been transmitted by transfusion of blood or blood products collected from donors during the viremic phase of their infection

Transmission of HAV by plasma derivatives in Europe and the U.S. has been well documented in the literature, including outbreaks of hepatitis A that were reported during the 1990's among persons with clotting-factor disorders who received solvent-detergent-treated factor VIII or factor IX concentrates from plasma donors incubating hepatitis A. Unfortunately, CDC does not collect data on the risk factors involved in its transmission and cannot assess the number of hepatitis A cases due to blood transfusions. However, analysis of the surveillance data collected in the Sentinel Counties Study of Acute Viral Hepatitis showed that of 3414 cases of acute hepatitis A reported from 1991-2001, only one (from 1996) reported a blood transfusion during the incubation period. Three other HAV cases occurred in the last 8 years in patients that received blood transfusions. These data seem to indicate that the incidence of hepatitis A transmission through blood transfusion is very rare.

At the December 4-5, 2001 FDA Workshop on "Application of Nucleic Acid Testing to Blood Borne Pathogens and Emerging Technologies," Source Plasma manufacturers, blood establishments, laboratory testers, developers of assays, and blood bankers presented data on their experience with HAV NAT and the incidence of reactive units. HAV NAT was performed in pools of 512 to 11,500 samples. Although there is a wide variation in pool sizes and sensitivities, the general conclusion was that the HAV NAT-reactive yield is relatively low with a range of 1 positive donation in 120,000 to 1,805,500 donations. Data using the most sensitive HAV NAT presented at the workshop suggest that approximately 1 in 10^5 donations contain HAV RNA and could potentially transmit the disease.

FDA's Current Thinking

The following points summarize FDA's current thinking on HAV NAT for Blood and Plasma. FDA is considering recommending that

- For Whole Blood donations, when feasible, HAV NAT reactive pools should be resolved to identify the individual reactive donors prior to release of components for transfusion, and that units from reactive donors should not be used for transfusion.

- When testing is done subsequent to product release, in-date components from potentially reactive donors should be retrieved and discarded so that they are not used for transfusion or further manufacturing into injectable products.
- Even when performed as an “in-process” test (i.e. not performed pre-release as part of a determination of donor suitability or product labeling), testing and identification of the individual reactive donor constitutes medical diagnostic testing. Therefore, such testing requires the use of an investigational test under an FDA approved investigational mechanism.
- Informed consent should be obtained from blood and plasma donors subjected to HAV NAT testing. Reactive donors should be identified, be informed of the reactive status, and be provided with medical counseling. Because of the transient nature of the infection and a rapid development of the immune response, such donors are suitable to donate when they test non-reactive.