

# **I. Plasma Pool Screening by Nucleic Acid Tests for Hepatitis A Virus**

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**66<sup>th</sup> Meeting  
June 15-16, 2000  
Holiday Inn, Silver Spring  
8777 Georgia Avenue  
Silver Spring, MD**

## **Blood Product Advisory Committee Meeting, June 15, 2000**

### **Plasma Pool Screening by Nucleic Acid Tests for Hepatitis A Virus**

#### **Introduction**

**FDA has received a submission from a manufacturer of plasma derivatives for plasma screening of minipools using nucleic acid tests (NAT) for hepatitis A virus (HAV) and human parvovirus B 19. Currently the Agency has articulated policies for NAT plasma pool testing for parvovirus B 19, human immunodeficiency virus (HIV), hepatitis B virus (HBV) and hepatitis C virus (HCV), but has not yet developed a policy in regard to HAV plasma pool testing.**

#### **Background**

**After public discussion at an open Blood Products Advisory Committee (BPAC) meeting in September, 1999, FDA, in accordance with the recommendations of BPAC, decided to regulate parvovirus B 19 NAT testing as "in process control" testing. In this case, if a minipool tests NAT B 19 positive, the positive pool is not used for the manufacture of plasma derivatives. No further action is taken, and those donors whose plasma units could have contributed to a pool's parvovirus B 19 NAT positivity are not identified. This is in contrast to FDA's position in regard to plasma pool screening for HIV, HBV and HCV by NAT. In these cases, FDA took the position that such testing constituted "donor screening" and that, in addition to removal of HIV/HBV/HCV NAT positive material from plasma derivative production channels, individuals whose units could have contributed to a pool's NAT positivity should be identified and informed about the positive test result.**

**The two different positions that FDA has taken in regard to NAT pool testing for**

- 1) parvovirus B 19 ("in process control" testing, no donor identification) and,**
- 2) HIV/HBV/HCV ("donor screening," donor identified),**

**were based on considerations, for each infection, of a) the medical benefit and technical feasibility of donor deferral, counseling, treatment, and avoidance of transmitting the disease to others; b) the medical benefit and technical feasibility of quarantining any unused, previously collected and possibly infected (window period) units from the donor; and c) the usefulness of notifying recipients of window period units, for purposes of possible treatment and avoidance of disease transmission to others. To perform this analysis, the length of the window period, the severity of infection and the likelihood of chronic infection of each disease was considered. These issues need to be examined for HAV NAT.**

## **Discussion**

**Hepatitis A infection is an acute, self-limiting infection of the liver. The infection may be asymptomatic or may cause an acute hepatitis syndrome of varying degrees of severity up to and including fulminant hepatitis. Older persons, pregnant women and persons with pre-existing liver disease, including from HCV, are at increased risk for severe HAV disease. The incubation period of the disease (from exposure to the development of clinical symptoms) varies from 2 to 8 weeks. This appears to argue in favor of retrieval of certain previously collected units from individuals who test HAV NAT positive, and to the deferral of such individuals from donation. The duration of symptoms may vary widely, but they usually last about 3 weeks. Recurrent forms of the disease have been reported recently, lasting up to about 400 days in about 3% of infections.**

**The disease is transmitted via the fecal-oral route. Post-exposure prophylaxis with Immune Globulin administered within two weeks of exposure can prevent or lessen symptoms. In principle, if informed promptly, a donor who tests HAV NAT positive might benefit from administration of Immune Globulin. However, this is not an established practice. Such a donor also could take steps to prevent HAV transmission to others, and close contacts (e.g., family members) could be given Immune Globulin. Inactivated-virus vaccines, which have been shown to be very effective when administered prior to exposure, are available in the U.S. (These vaccines are being considered for their use in the post-exposure setting.) It is recommended that anyone who is a regular recipient of blood or plasma products be vaccinated.**

**Extremely few transmissions of HAV by transfused blood have been reported in the world literature. This appears to argue against the value of notifying recipients of transfused components previously collected from individuals who test HAV NAT positive.**

**Transmission of HAV by plasma derivatives is not a major clinical problem, but it can occur. While plasma derived volume expanders (albumin and PPF) and immunoglobulins historically have been safe, there have been reports of HAV transmission by Factor VIII and Factor IX. Note that solvent detergent treatment, used widely to inactivate lipid-enveloped HIV, HBV and HCV during the manufacture of plasma derivatives, does not inactivate non lipid-enveloped viruses such as HAV.**

## **FDA's Current Thinking**

**FDA considers that performance of validated HAV NAT on plasma minipools can enhance the margin of safety for plasma derivatives. Thus, we encourage the adoption of plasma pool testing that would lower the viral burden of pathologic**

**viruses in manufacturing pools, and hence increase the safety of plasma derivatives. Additionally, the Agency is of the opinion that a donor whose plasma could have caused a plasma pool to test HAV NAT positive, and whose retained, unpooled sample from the implicated unit tests HAV NAT positive, should be informed about the positive test results, and that unpooled units from collections in the last 3 months should be retrieved and destroyed. (Note that hepatitis A is a reportable disease in most states and that notification should be made to the state health department.) Also, the donor should be deferred from donating for 3 months. FDA does not believe that recipient tracing and notification is necessary or that individual donations should be screened by HAV NAT.**

**If FDA were to adopt its current thinking as a policy, FDA would regard HAV NAT as a donor screen, but would hold it to an approved standard as a medical device, similar to the current approach toward voluntary use of ALT and CMV tests. As a practical matter, approval would be based on manufacturing validation, pre-clinical testing and limited clinical studies.**