

75th Blood Products Advisory Committee Meeting – December 12, 2002

Parvovirus B19 NAT for Whole Blood and Source Plasma

Issues

FDA is seeking advice (1) whether the risks of parvovirus B19 infection to transfusion recipients are sufficient to warrant withholding high-titer ($> 10^6$ geq/mL) B19 NAT-positive units of Whole Blood and transfusable components from use; (2) whether such high-titer donors should be temporarily deferred; and (3) whether potential medical benefits to close contacts, especially those at risk, of B19 infected donors warrant identification and notification of positive donors.

Background

Consistent with the advice provided by the BPAC (September 1999), FDA has allowed testing of plasma pools (“minipools”) for parvovirus B19 by NAT to ensure the quality of Solvent/Detergent Treated Pooled Plasma and Source Plasma to be regarded as “in-process” testing rather than donor screening. Test results were used to reject reactive units (or units represented in positive minipools), and donors were not notified or deferred. BPAC did not recommend resolving the reactive pool to the individual donor. FDA has reviewed 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.

For several years, Source Plasma fractionators have been performing minipool testing on donated units at sensitivities sufficient to lower the viral levels in the manufacturing pools to below a theoretical level of concern of 10^4 geq/mL. Fairly insensitive assays are used that will detect only high titer units. Additionally, fractionators are resolving reactive minipools to individual donations. Even though test methods and their sensitivities may vary, results from such tests have been used to reject reactive units. However, positive donors have not been notified or deferred.

More recently, establishments collecting Whole Blood (used both to prepare recovered plasma for further manufacturing use and to provide transfusable components) would like to implement B19 NAT screening similar to that used by Source Plasma fractionators, i.e., screening only to detect high titer units. 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 are not feasible for blood components because an appropriate technology infrastructure is lacking. However, minipools would eventually be resolved to positive units prior to release (similar to the procedures in place for HIV-1/HCV NAT assays).

The viremic levels in acutely infected and often asymptomatic donors can be extremely high, i.e., $> 10^{12}$ geq/mL. These donors would be detected by currently available tests.

However, FDA understands that such high-titer, i.e., insensitive, screening may not capture all infectious donors and hence potentially infectious products, especially unpooled blood components. B19 DNA after acute infection can persist albeit at low levels for up to 1 year or longer in immunocompetent individuals. The infectivity is largely dependent on the balance between virus and the presence of anti-B19 antibodies (which can potentially complex with or neutralize the virus). If an overly sensitive B19 NAT assay is used to reject units with low-level B19 DNA and anti-B19 IgG antibody, the consequence may be a reduction in effective anti-B19 levels in plasma pools and this could reduce the safety of the resulting derivative products.

At the March 2002 BPAC meeting FDA presented its current thinking on parvovirus B19 NAT for Blood and Plasma. The following recommendations that FDA is considering were presented:

1. When identified, high-titer parvovirus B19 reactive plasma donations should not be used for further manufacturing into injectable products. This is to ensure that the FDA's proposed limit, $<10^4$ IU of B19 DNA/mL, for manufacturing pools destined for making plasma derivatives can be met.
2. For Whole Blood donations, when feasible, B19 reactive minipools should be resolved to identify the individual reactive donors prior to release of components for transfusion, and units from reactive donors should not be used for transfusion. ("Reactive" implies having a titer that is above a pre-established, appropriately high threshold.)
3. 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.
4. 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 would require the use of an investigational test under an FDA approved investigational mechanism.
5. Informed consent should be obtained from Blood and Plasma donors subjected to such NAT testing. Reactive donors should be identified, be informed of their 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 would be suitable to donate when they test non-reactive.

Committee discussions at the March 2002 BPAC meeting largely focused on an apparent lack of medical benefits that might justify donor notification. This discussion prompted the FDA to convene a PHS panel (Participants: Drs. Harvey Klein, Kevin Brown, Mary Chamberland, Larry Anderson, Bruce Evatt, and CBER representatives) to discuss

medical issues relevant to B19 NAT. The PHS panel discussion was held on July 12, 2002 and reached the consensus summarized below:

1. Regarding the **donors**, there is **no** medical benefit in identifying high-titer B19 NAT positive donors, informing them of their reactive status, and providing medical counseling.
2. Regarding **close contacts** of the high-titer B19 NAT positive donors, there are potential medical benefits to donors' contacts, especially those at risk, e.g., persons with certain anemias, pregnant women, and immune deficient (suppressed or compromised) individuals.
3. There is an ethical obligation to notify donors of their high-titer B19 NAT positive status.

Discussion of the Issues

FDA is taking a step-wise approach in resolving B19 NAT issues concerning Whole Blood and Source Plasma. At this BPAC meeting, the focus is on resolving the following medical and scientific issues:

1. FDA is seeking advice from the BPAC whether, for Whole Blood donations, there are sufficient risks to transfusion recipients to warrant withholding high-titer individual positive units ($\geq 10^6$ geq/mL), prior to release of blood components for use in transfusion. Items to be considered in arriving at a decision include the following:
 - ?? There is no definitive information yet regarding the precise, minimal B19 viral load in blood components or plasma that can transmit infection to recipients, especially in unpooled products. However, B19 is known to have high tropism to erythroid progenitor cells, such as those present in bone marrow and fetal liver. Based on available literature, high-titer units, with $\geq 10^6$ geq/mL, could almost certainly be infectious. To minimize the risk of infection in recipients and to prevent serious consequences of B19 infections in high risk recipients, e.g, pregnant women, persons with certain anemias, and immune compromised individuals, FDA believes that it is desirable to withhold these high-titer donations.
 - ?? A screening threshold lower than 10^6 geq/mL may be appropriate for removing transfusable Whole Blood and components from use. However, the B19 viral level that correlates with infectivity of a unit is unknown.
 - ?? B19 DNA can persist at low levels in immune competent individuals for a very long time. Before the appropriate threshold is established, withholding low viral titer donations by sensitive NAT may result in rejection of units that are non-infectious and which contain protective antibody. Thus, units may be

- unnecessarily discarded. Clinical evidence of a significant risk from transfusion is lacking despite absence of screening at the present time.
2. A temporary deferral may be warranted for high-titer donors of Whole Blood and Source Plasma if positive donations can be resolved within several weeks.
 - ?? It is anticipated that invited speakers will provide data regarding such points as the time to resolve to single positive donors, their viremic levels/antibody status, and the profiles of B19 DNA and anti-B19 antibodies in subsequent serial bleeds. Because of the transient nature of the B19 infection and a rapid development of the immune response, protracted deferral of such donors may not be warranted.
 - ?? Reactive apheresis donors could donate several units before the viral levels drop. It may be appropriate to defer such donors for a short time period.
 3. FDA is seeking the BPAC's opinion on the recommendations made by the PHS panel mentioned above, i.e., that there are sufficient potential medical benefits to close contacts, but not to donors, to warrant notification of parvovirus B19 positive donors. Items to consider include the following:
 - ?? There may be no medical benefit in notifying positive donors. B19 infection in otherwise healthy donors is often mild and is asymptomatic in most cases. By the time individual positive donors have been identified, they may no longer be infectious and there is no effective medical intervention.
 - ?? There may, however, be potential medical benefits to donors' close contacts who are at risk. B19 can cause extensive fetal damage and severe disease or even death in immune compromised individuals. At-risk individuals that have been exposed to high-titer donors may derive benefit from medical intervention, e.g., by treatment with IGIV if it is given soon enough (although this is an off-label use of IGIV). Since B19 is known to transmit via the respiratory route, avoiding exposure of such close contacts as pregnant women and immune compromised individuals would be expected to be beneficial. Notification of the donor could be the first step in identifying and notifying close contacts.
 - ?? Donor notification for the purpose of reaching close contacts is likely to be useful only in settings where testing and notification can be completed within several (e.g. less than four) weeks of donation.

Questions for the Committee

1. If donations of Whole Blood are tested for presence of human parvovirus B19, are risks to transfusion recipients sufficient to warrant withholding high titer positive units ($\geq 10^6$ geq/mL) from use for transfusion?

2. Is temporary deferral of positive donors warranted in the setting of
 - a. Whole Blood donation?
 - b. Apheresis donation?
3. Do potential medical benefits to contacts of parvovirus B19 infected donors warrant identification and notification of positive donors?
4. If yes to question 3, should donor notification be limited to settings where testing and notification can be completed within several weeks of donation?