Update on FDA NAT Guidance: Parvovirus B19

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Guidance for Industry
“Nucleic Acid Testing (NAT) to Reduce the Possible Risk of Human Parvovirus B19 Transmission by Plasma-Derived Products”

• Draft guidance was first published in July 2008.
• Final guidance was issued in July 2009.
Outlines the FDA’s current thinking on B19 NAT

- Recommends that manufacturers of plasma-derived products perform B19 NAT as an in-process test for Source Plasma and recovered plasma used for further manufacturing

- Explains how to report such implementation to FDA

- Encourages manufacturers to reduce the time between plasma collection and in-process NAT testing to allow for the meaningful notification of blood and plasma collection establishments of positive test results within the dating period of any blood components intended for use in transfusion.
B19 is a small, non-enveloped, single-stranded DNA virus. 

- Resistant to common viral inactivation methods
  - S/D or heat treatment
    (but recent studies demonstrate that B19 may be more susceptible to heat or low pH treatment than certain model animal parvoviruses)

- Difficult to remove by filtration because of its small size
• B19 may cause morbidity to susceptible recipients, such as pregnant women (and their fetuses exposed in utero), persons with underlying hemolytic disorders, and immune compromised individuals.

• Disease transmission by transfusion of blood components is rare. However, extremely high levels (~$10^{12}$ IU/mL) of B19 DNA in plasma of acutely infected but asymptomatic donors may present a greater risk in plasma derivatives due to pooling of large numbers of plasma units during manufacture.
FDA has held or participated in several meetings to discuss the potential risk of B19 infection by plasma-derived products and strategy for reducing such risk

- Sep 1999 Blood Products Advisory Committee (BPAC)
  - Safety of Pooled Plasma S/D Treated correlated with those lots having $<10^4$ geq/mL of B19 DNA in manufacturing pool (a phase 4 study).
  - For plasma for further manufacturing, B19 NAT screening was recommended as an in-process test.
  - In-date (+) blood components were recommended to be quarantined and destroyed when possible.

- Dec 1999 FDA NAT Workshop
  - The possibility of limiting $<10^4$ geq/mL of B19 DNA in all manufacturing pools was discussed.
FDA B19 NAT Guidance - Background (IV)

- Dec 1999 NHLBI Parvovirus B19 Workshop
  • FDA’s in-process B19 NAT standard for plasma for further manufacturing was presented.

- Dec 2001 FDA NAT Workshop
  • Proposed limit: $<10^4$ IU/mL of B19 DNA in all manufacturing pools (availability of the 1st B19 WHO International Standard)

- Mar 2002 BPAC
  • FDA’s current thinking on B19 NAT for Blood and Plasma

- Jul 2002 Ad Hoc PHS Panel
  • Medical benefits to donors and close contacts

- Dec 2002 BPAC
  • B19 NAT issues concerning Whole Blood and Source Plasma
• A common recommendation for mitigating the risk of B19 transmission by plasma derivatives from those meetings mentioned above
  – Limit the viral load in the manufacturing pool by using a minipool screening format to detect and thus exclude high-titer B19 donations, in combination with the ability of the manufacturing procedures to clear the residual virus
    • Excluding donations with low levels of B19 DNA, which often co-circulates with anti-B19 IgG (which can potentially complexing with and neutralize the virus) may adversely affect anti-B19 levels in pools and resulting plasma derivatives

• The recommended viral load limit in manufacturing pool, i.e., not to exceed $10^4$ IU/mL, was primarily derived from the B19 transmission associated with S/D Treated Pooled Plasma
FDA B19 NAT Guidance - Recommendations (I)

• For all plasma-derived products, perform B19 NAT as an in-process test to ensure that the viral load of B19 DNA in the manufacturing does not exceed $10^4$ IU/mL.

• Use minipool samples to screen plasma units intended for further manufacturing. Primers and probes selected for B19 NAT should detect all known genotypes of the virus.

• Do not use those individual units having a titer of B19 DNA that might result in manufacturing pools exceeding $10^4$ IU/mL.
FDA B19 NAT Guidance - Recommendations (II)

- Assess validation data demonstrating accuracy, sensitivity, specificity, reproducibility, and other performance characteristics of the B19 NAT assays used for detecting B19 DNA in Source Plasma and recovered plasma.

- Demonstrate that the viral load in the manufacturing pool does not exceed $10^4$ IU/mL.

- When implemented, must inform FDA, as required under 21 CFR 601.12(a). To an approved application, submit as a “Supplement-Changes Being Effected” (CBE supplement) under 21 CFR 601.12 (c)(5).