CHAPTER 7

Infectious Disease Screening

Lauren A. Crowder, MPH; Whitney R. Steele, PhD, MPH; and Susan L. Stramer, PhD

BLOOD COMPONENTS, LIKE ALL OTHER medications in the United States, are regulated by the Food and Drug Administration (FDA). The FDA requires drug manufacturers to verify the suitability of every raw material in their products.[1] For biologic pharmaceuticals, the donor is the key ingredient whose suitability must be verified.

A sample of blood from each donation must be tested with screening tests approved by the FDA to identify donors and donated components that might harbor infectious agents. This screening process is critically important because most blood components (eg, red cells, platelets, plasma, and cryoprecipitate) are infused without other treatments to inactivate infectious agents. Thus, infectious agents in a donor's blood at the time of donation that are not detected by the screening process may be transmitted directly to recipients.

HISTORICAL OVERVIEW OF BLOOD DONOR SCREENING

Table 7-1 shows the progression over time of donor testing for infectious diseases in the United States. Initially, donors were screened only for syphilis. In the 1960s, studies showed that greater than 30% of patients who received multiple transfusions developed posttransfusion hepatitis (PTH).[2] Studies in the early 1970s found that the newly discovered hepatitis B virus (HBV) accounted for only 25% of PTH cases.[2] Both HBV and non-A, non-B (NANB) hepatitis occurred more frequently in recipients of blood from commercial (paid) blood donors than in recipients of blood from volunteer donors. By the mid-1970s, implementation of sensitive tests for hepatitis B surface antigen (HBsAg) and conversion to a volunteer donor supply resulted in a dramatic reduction in the incidence of both HBV and NANB PTH. Still, NANB PTH continued to occur in approximately 6% to 10% of recipients of multiple transfusions.[2,3]

In the absence of a specific test for the causative agent of NANB PTH, investigators searched for surrogate markers that could be used to identify donations associated with NANB hepatitis. The presence of antibody to hepatitis B core antigen (anti-HBc) and/or the presence of elevated alanine aminotransferase in blood donors was shown to be associated with an increased risk of NANB PTH.[4-7] However, concerns about the nonspecific nature of these tests led to a delay in their implementation for donor screening.

The concept of surrogate testing was revisited in the early 1980s when concerns arose about the transmission of AIDS by transfusions before the identification of its causative agent. In an effort to reduce the potential transfusion transmission of AIDS, some blood banks implemented donor testing for anti-HBc, because this antibody was highly prevalent in populations at increased risk of AIDS, and/or donor screening

Lauren A. Crowder, MPH, Epidemiologist, Scientific Affairs, American Red Cross, Rockville, Maryland; Whitney R. Steele, PhD, MPH, Director of Epidemiology, Scientific Affairs, American Red Cross, Rockville, Maryland; and Susan L. Stramer, PhD, Vice President, Scientific Affairs, American Red Cross, Gaithersburg, Maryland

The authors have disclosed no conflicts of interest.

TABLE 7-1. Changes in Licensed US Donor Screening Tests for Infectious Diseases

Year First Implemented	Screening Test	Comments
1940s-1950s	Syphilis	The syphilis test was mandated by FDA in the 1950s.
1970s	HBsAg	The first-generation test was available in 1970, and a higher-sensitivity test was required in 1973.
1985	Antibody to HIV (anti-HTLV-III)	The initial name for HIV, the virus that causes AIDS, was HTLV-III. The first test for antibody to HIV was called "anti-HTLV-III."
1986-1987	ALT and anti-HBc	ALT and anti-HBc were recommended by AABB as surrogate tests for NANB hepatitis. These tests were initially not licensed by FDA for donor screening. AABB's recommendation for donor ALT testing was dropped in 1995 after antibody testing for HCV was in place. Anti-HBc was licensed and required by FDA in 1991.
1988	Anti-HTLV-I	Although HTLV-I infection is usually asymptomatic, a small percentage of infected individuals develop leukemia, lymphoma, or a neurologic disease.
1990	Antibody to HCV, Version 1 (anti-HCV 1.0)	HCV was identified as the cause of most cases of NANB hepatitis.
1991	Anti-HBc	Anti-HBc was previously recommended by AABB as a surrogate screen for NANB hepatitis. It was required by FDA in 1991 as an additional screen for HBV.
1992	Anti-HCV 2.0	This version had improved ability to detect antibody to HCV.
1992	Anti-HIV-1/2	The new HIV antibody tests had improved ability to detect early infection and an expanded range of detection that included HIV-2 in addition to HIV-1.

1996	HIV-1 p24 antigen test	This test was found to detect HIV-1 infection 6 days earlier than the antibody test. FDA permitted discontinuation of HIV-1 p24 antigen testing with the implementation of a licensed HIV-1 NAT.
1996	Anti-HCV 3.0	This version has improved ability vs anti-HCV 2.0 to detect antibody to HCV.
1997-1998	Anti-HTLV-I/II	The new HTLV antibody tests detected HTLV-II in addition to HTLV-I.
1999	HIV-1 and HCV NAT to detect HIV and HCV RNA	These tests were implemented initially as investigational assays and were licensed by FDA in 2002. They detect infection earlier than antibody or antigen assays and are performed using MP-NAT in pools of 6-16.
2003	West Nile virus NAT to detect WNV RNA	This test was implemented initially as an investigational assay and was licensed by FDA during 2005-2007. Testing by ID-NAT, rather than MP-NAT, at times of increased WNV activity in a region was recommended by AABB in 2004 and FDA in 2009. Updated AABB recommendations were issued in 2013.
2004	Sampling of platelet components to detect bacterial contamination	Testing was recommended by AABB in 2004. Some tests are approved by FDA as quality-control tests. Since 2011, AABB has accepted only FDA-approved tests or those validated to have equivalent sensitivity. Pathogen-reduced platelets meet the AABB requirement.
2006-2007	Antibody to *Trypanosoma cruzi*	This test was approved by FDA as a donor screen late in 2006, and widespread testing was implemented in 2007. The rarity of seroconversion in US residents led to endorsement in FDA 2010 guidance of one-time donor screening.
2007-2008	HBV NAT to detect HBV DNA	This test was initially implemented as part of automated multiplex assays that detect HIV RNA, HCV RNA, and HBV DNA simultaneously. HBV DNA screening was explicitly recommended by FDA guidance issued in October 2012. Testing is performed using MP-NAT in pools of 6-16.

(Continued)

TABLE 7-1. Changes in Licensed US Donor Screening Tests for Infectious Diseases (Continued)

Year First Implemented	Screening Test	Comments
2016	ZIKV NAT to detect ZIKV RNA	Universal ID-NAT was recommended by FDA guidance issued in August 2016 in response to the epidemic in the Americas (with immediate implementation in Puerto Rico, 4-week implementation in high-risk Southern states and New York, and 12-week implementation in all other states). Guidance released in July 2018 allows the use of MP-NAT in place of ID-NAT (in pools of 6-16), unless a region is experiencing a local outbreak in which ID-NAT must be used. Licensed pathogen inactivation may be used in place of testing.
2019	*Babesia* NAT to detect *B. microti* DNA/RNA	This NAT assay was licensed and mandated for use in 2019. Licensed pathogen inactivation may be used in place of testing. No licensed serologic assay is available.

FDA = Food and Drug Administration; HBsAg = hepatitis B surface antigen; HIV = human immunodeficiency virus; AIDS = acquired immune deficiency syndrome; HTLV = human T-cell lymphotropic virus; ALT = alanine aminotransferase; HBc = hepatitis B core antigen; NANB = non-A, non-B; HCV = hepatitis C virus; HBV = hepatitis B virus; RNA = ribonucleic acid; NAT = nucleic acid testing; MP-NAT = minipool nucleic acid testing; ID-NAT = individual donor nucleic acid testing; WNV = West Nile virus; DNA = deoxyribonucleic acid; ZIKV = Zika virus.