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Is HBsAg screening still necessary for Source Plasma: A risk analysis

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Introduction

- Blood services are required to test donations for HBV through a combination of nucleic acid tests (NAT), serological tests (anti-HBc), and antigen tests (HBsAg).
  - However, the rationale for mandatory HBsAg testing appeared increasingly questionable with recent studies showing that it offers little to no safety gains compared with a strategy consisting of NAT and anti-HBc testing alone.

- In a draft guidance document issued in July 2025, the US Food and Drug Administration (FDA) revisited this requirement and recommended that the requirement to test all blood and blood components for HBsAg be lifted.
  - However it proposed that mandatory HBsAg testing be maintained for Source Plasma, citing a lack of data on HBV screening tests and the absence of anti-HBc tests for Source Plasma donations.

Introduction

Recommendations for Testing Blood Donations for Hepatitis B Surface Antigen

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Draft Guidance for Industry

This guidance recommends that when donations, other than for Source Plasma, are tested for HBV DNA by nucleic acid tests (NAT) and for antibody to hepatitis B core antigen (anti-HBc) using screening tests that FDA has licensed, approved, or cleared for such use, in accordance with the manufacturer's instructions, testing for HBsAg is not necessary to reduce adequately and appropriately the risk of transmission of HBV. We have not changed our recommendations with respect to HBsAg testing for Source Plasma; our thinking continues to be that testing of Source Plasma donations for HBsAg and HBV DNA by NAT is necessary to reduce adequately and appropriately the risk of transmission of HBV.

FDA's rationale to continue testing HBsAg for source plasma

In contrast, a consideration to eliminate HBsAg testing in the absence of anti-HBc test results, when HBV NAT is performed, is not supported by these data (Refs. 5-6). For example, in one study of volunteer blood donors, 13% of HBV infected donations were detected by HBsAg but were missed by HBV NAT screening (i.e., donations were reactive for HBsAg and nonreactive for HBV DNA by minipool testing) (Ref. 6).

- However, the cited study by Dodd, RY, et al., 2018 found only 6 HBsAg-positive and MP-NAT/anti-HBc-negative donations out of 22.4 million donations screened and 2035 infected donations by the American Red Cross. These six HBsAg yield donations likely contained extremely low or negligible levels of HBV DNA.

In Germany, approximately 45 million blood donations were screened between 2008 and 2015 and only one donation was identified that was HBsAg positive with low-level HBV DNA detectable by ID-NAT on further investigation, but negative by MP-NAT and anti-HBc screening tests (Ref. 9). Thus, the individual contribution of the HBsAg screening test for yield donations in this study was 1 in 45 million. In contrast, NAT identified 29 cases of HBV infection that were nonreactive for HBsAg or anti-HBc.

The only donation is identified with extremely low concentration and the risk didn't consider the effect of fractionation on HBV viral loads.

Introduction

- Yet HBsAg-positive/mini-pool (MP)-NAT-negative donations are exceedingly rare (<1 in 1 million donations) and so the associated risk may be very small.
  - Moreover, Source Plasma manufacturing pools undergo viral inactivation in addition to bulk fractionation and protein purification steps; collectively, these steps are highly effective at inactivating residual pathogens, with log-reduction factors of 9.1 – >12.
  - Therefore, even without HBsAg testing, the probability that a vial of plasma-derived product contains an infectious dose of HBV is probably extremely low. However, this has never been quantified.

- Our aim was to address this knowledge gap by estimating the residual HBV viral loads in a vial of plasma-derived product prepared from a contaminated plasma pool, in the absence of HBsAg screening.

Risk of fractionating an infected source plasma pool if HBsAg testing is not performed.

Methods

- This was a deterministic model that assessed the HBV viral loads in a vial of human fibrinogen concentrate (HFC) produced from a plasma pool containing one single HBV-infected donation.

- HFC was conservatively selected because this product has the lowest log-reduction factor (≥9,1) compared to other plasma-derived products.

Assumptions

- All units would still be screened using NAT in minipools of 16.
- Some infectious units might be missed by MP-NAT due to the assay's limit of detection (LOD).
- We assumed that all confirmed HBsAg-positive units are infectious. In other words, we did not account for the possibility that some HBsAg-positive units might contain defective, non-infectious viral particles.
- We assumed that the presence of ≥1 viral particle in a product vial would be sufficient to transmit HBV. We neither considered the neutralizing effects of anti-HBs in the plasma pools nor the fact that many recipients may be immune to HBV.

Model steps

- Probability of encountering an HBsAg-positive-only plasma donation
- Maximum viral load in an HBsAg-positive/MP-NAT-negative donation
- Maximum viral load in a plasma volume used to produce one vial of RiaSTAP (based on lowest log reduction factor)
- Log reduction factor and safety margin

Probability of Identifying an HBsAg-Positive and MP-NAT-Negative Plasma Donation

Total Number of Plasma Donations	22 370 273
Number of Donations Identified as HBsAg-Positive and MP-NAT-Negative	6
Probability of encountering a plasma donation HBsAg+ AND MP-NAT-	**2,68213E-07**

TABLE 2. Comparison of data trends (number and rates), 2009-2011 (prior study, Stramer et al.[1]) with 2011-2015 (current study)

	2009-2011		2011-2015	
	Number	Rate pht	Number	Rate pht
Tested	12,772,651		22,370,273	
Active infection	1,368	10.7	2,035	9.1
MP NAT positive (total)	941	7.4	1,453	6.5
OBI (MP-NAT negative)	238	1.9	361	1.6
OBI (MP-NAT positive)	35	0.27	43	0.19
OBI total	273	2.17	404	1.81
HBsAg positive (total)	1,090	8.5	1,602	7.2
HBsAg yield	25	0.20	35	0.16
HBsAg only	2	0.02	6	0.03
DNA NAT yield	5	0.04*	29	0.13*
Incidence (phtpy)†		1.62		1.30

* $p < 0.01$.
† phtpy = per hundred-thousand person-years.

TABLE 1. Results of additional testing of six HBsAg-reactive, anti-HBc–nonreactive samples with low-level HBV DNA

Sample ID	Anti-HBc	Anti-HBs IU/L	HBsAg S/CO			Neutralization	NAT	MP-NAT	No. dHBV test positive/ No. tested	Donation status (FT/RPT)	Age (years)	Sex	Race
006LP	N	NT	1.79	1.66	1.60	NT	Ultrio	N	1/1	FT	22	Female	Caucasian
007FQ	N	NT	4.10	3.99	3.86	NT	Ultrio	N	1/1	FT	16	Female	Non-Caucasian
011LS	N	>400	1.02	1.32	1.49	P	Ultrio	N	1/10, 0/10	RPT	28	Female	Unknown
Retest			3.60	1.87	1.93								
032KS	N	<5	1.14	1.17	1.11	P	Ultrio	N	1/10, 0/10	RPT	30	Female	Non-Caucasian
Retest			0.92										
W0255	N	<5	2.39	2.54	2.61	P	Ultrio Plus	N	4/10, 0/10	RPT	19	Male	Caucasian
Retest			1.71	1.62	1.49								
041FQ Retest	N	<5	1.45	1.31	1.34	P	Ultrio	N	6/10, 9/10	RPT	56	Male	Non-Caucasian

dHBV = Ultrio Plus discriminatory NAT; FT/RPT = first-time or repeat donor; N = negative; NT = not tested; P = positive.

Dodds et al. 2018. Transfusion

Maximum viral load in an HBsAg+/MP-NAT- donation

Information about the MP-NAT test		
LOD95 (in IU/mL)	3,4	[A]
LOD95 (in copies/ml)	17	[B] = [A] x 5
Nb donation per pool	16	[C]
Maximum viral load in a donation during the window period (MP-NAT-)		
Diluted LOD95 (in copies/ml)	272	[D] = [B] x [C]

FIGURE 2 Viral load distribution for HIV, HBV, and HCV (after seroconversion). HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus.

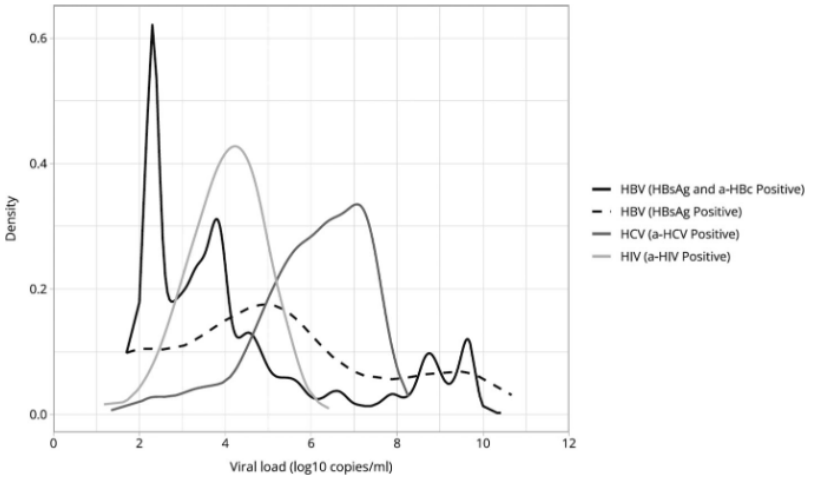

TABLE 3 Limit of detection and sensitivity of assays.

	HIV	HBV	HCV	Reference
LOD_{50} NAT (IU/mL)	4.7	0.7	1.2	30
LOD_{95} NAT (IU/mL)	21.2	3.4	5.4	30
Conversion factor (IU per mL to copies per mL)	0.6	5	3.4	30
Sensitivity NAT Ultrio Plus[a] (%)	100.0 (98.2–100.0)	100.0 (98.4–100.0)	99.0 (96.4–99.9)	30
Sensitivity anti-HIV, anti-HBc, anti-HCV[a] (%)	100.0 (99.8–100.0)	99.49 (98.8–99.8)	100.0 (99.5–100.0)	28,31,32
Sensitivity anti-HBc (occult)[a] (%)	-	77.0 (62.0–88.0)	-	14
Sensitivity HBsAg[a] (%)	-	100.0 (99.5–100.0)	-	33

Abbreviations: HBC, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; LOD, limit of detection; NAT, nucleic acid test.
[a]Uncertainty modeled with a beta distribution.

Domingue et al. 2024. Transfusion

Maximum Viral Load in a Plasma Volume Used to Produce One Vial of RiaSTAP (Based on Lowest Log Reduction Factor)

Maximum viral load for one infected donation (i.e. <LOD95)	272	[A]	copies/ml
Probability of having an infected donation HBsAg + and MP-NAT-	2,68213E-07	[B]	
Number of donations needed for a volume of plasma to produce one pool of plasma (23 000L)	32,857	[C] =23 000/0.700	≈700mL/donation
Probability of having an infected donation in the plasma pool	0,008812716	[D] = [B] x [C]	
Number of pool needed to have an infected pool by one donation	113	[E] = 1/[D]	
Maximum virus count in a volume of plasma (23 000L) - Worst case assuming that all pools are infected with one donation	190,400	[F]=[A] * 700	≈700mL/donations
Conversion factor copie to IU	5	[G]	5 copie/IU
Maximum virus count in a pool of plasma (23 000 L) [IU]	38,080	[H]= [F]/[G]	
Maximum virus count in a volume of plasma needed to produce one vial of product (11.0 L) [IU]	18.21	[I]=([H]x11)/23000	IU in the total volume to produce one vial
Maximum virus count in a volume of plasma needed to produce one vial of product (11.0 L) [log_{10} IU]	**1.2604**	**[J]**	**log_{10} IU**

Log reduction factor and safety margin

Maximum virus load in a volume of plasma needed to produce one vial of product (11.0 L) [log_{10} IU]	1.2604	[A]	log_{10} IU
HBV log reduction factor for RiaSTAP® [log_{10}]	9.1	[B]	CSL personal communication
Safety margin log_{10} Viral count	(7.84)	[C]=[B] – [A]	log_{10} UI
Safety margin in viral count	69,125,488.14	[D]=$10^{[C]}$	UI

CSL Behring **Statement**

From	Duo Li, PhD
Document No.	GPSS_2019035_01_01
Organization	Global Pathogen Safety Support
Date	11 April 2019
Subject	**Pathogen Safety Evaluation for Toll Manufacture of Privigen®, Hizentra®, Alburex® 5, Alburex® 25, Humate-P®, RiaSTAP® for Canadian Blood Services**

1. Introduction

At the request of Canadian Blood Services, this document summarizes the pathogen safety information relating the toll manufacture of Privigen®, Hizentra®, Alburex® 5, Alburex® 25, Humate-P® and RiaSTAP®, presenting the validated overall log reduction factors (LRFs) for HBV, HCV and HIV, as well as the corresponding residual risk calculations.

2. Pathogen Safety Evaluation

Table 1 shows the overall mean LRFs for the plasma-derived products Privigen®, Hizentra®, Alburex® 5, Alburex® 25, Humate-P® and RiaSTAP®. These LRFs are based on virus validation studies (see Canada Certified Product Information Document [1][2][3][4][5][6]).

Table 1: Overall Mean Log Reduction Factors

	HBV [a]	HCV [b]	HIV
Privigen®	≥ 17.7	≥ 12.1	≥ 15.3
Hizentra®	≥ 17.7	≥ 10.9	≥ 15.3
Alburex® 5	15.33	19.08 [d]	12.91
Alburex® 25	14.65	19.26 [d]	12.30
Humate-P®	11.8	≥ 13.0	≥ 12.2
RiaSTAP®	≥ 9.1 [c]	≥ 11.2	≥ 9.6

[a] model virus PRV
[b] model virus BVDV
[c] model viruses PRV and HSV-1
[d] model viruses BVDV and SINV

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Discussion

- Under a conservative scenario where plasma pool is contaminated by one HBsAg-only positive and MP-NAT negative donation (approximately 32 857 donations—representing 23,000 liters of plasma), an exceptionally high safety margin has been achieved for hepatitis B virus (HBV).
- To produce a single product vial, a safety margin of 7.84 $\log_{10}$ has been demonstrated, corresponding to a 99.99999669% decrease. This means that only one viral particle remains out of approximately 70 million. To further illustrate this point, a viral concentration exceeding 69,125,488 IU would be required in 11 liters of plasma to detect a single infected vial—an event that is mathematically impossible under realistic conditions.
- Using a Poisson distribution with a mean viral load of λ = 2,380 IU (based on a LOD_{95} of 3.4 IU/mL in 700 mL donation), the probability of observing more than 69,125,488 IU is effectively zero: $P(X > 69{,}125{,}488) \approx 0$
- This result confirms that the likelihood of encountering such a high viral load is mathematically zero, reinforcing the extraordinary robustness of the safety margin.
- **In addition, such high viral loads simply cannot be missed by modern NAT technologies.**

Discussion

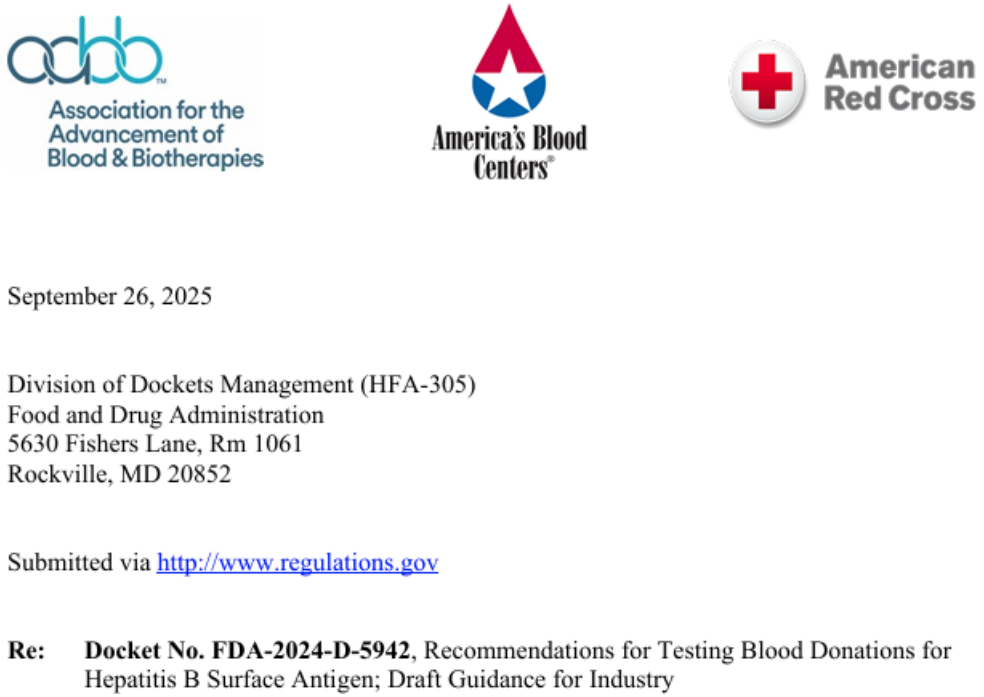
- Even then, our analysis assumes that HBsAg-positive/MP-NAT-negative donors are infectious, which may not always be the case.
  - A proportion of such donors are in fact expressing a truncated form of HBsAg due to HBV DNA integration, but these donors are not infectious, as the integrated form of the DNA is replication-incompetent.
  - Moreover, the correlation between HBsAg and viral replication in HBeAg-negative individuals is poor.
  - Therefore, most HBsAg-positive/MP-NAT-negative donors will not be infectious, and the true risk of transfusion-transmission is likely lower than that estimated herein.

Discussion

- What is more, plasma-derived products contain a host of antibodies, including some directed against HBsAg.
  - These antibodies bind the ‘a’ determinant conformational epitope, thereby neutralizing HBV particles and protecting against infection.
  - This consideration—which is absent for blood and blood components—probably further lowers the risk for Source Plasma donations.

- We conclude that the combination of HBsAg/MP-NAT offers no safety gains compared with MP-NAT alone for the testing of Source Plasma donations for HBV.

Conclusion



Association for the Advancement of Blood & Biotherapies

America's Blood Centers

American Red Cross

September 26, 2025

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm 1061
Rockville, MD 20852

Submitted via http://www.regulations.gov

Re: **Docket No. FDA-2024-D-5942**, Recommendations for Testing Blood Donations for Hepatitis B Surface Antigen; Draft Guidance for Industry

- The FDA does not agree with the AABB TTD's comments on eliminating HBsAg testing requirements across all plasma types, recognizing HBV NAT and Pathogen Inactivation as sufficient safeguards.
- Remaining question: How should we manage recovery plasma (i.e., plasma for further manufacturing that is not labeled as Source Plasma) for which HBsAg testing is no longer necessary?

QUESTIONS?

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