

IV. Hepatitis B Virus Nucleic Acid Testing (NAT) for Donors of Whole Blood

Issue Summary
Blood Products Advisory Committee Meeting
July 22-23, 2004

Topic IV: Hepatitis B Virus Nucleic Acid testing (NAT) for Donors of Whole Blood

Issue:

FDA seeks the opinion of the Committee on the performance of the Roche COBAS AmpliScreen HBV test in minipools of 24-samples to screen blood for transfusion by nucleic acid testing (NAT), and its proposed intended use as an alternative to hepatitis B surface antigen (HBsAg) testing in conjunction with testing for antibodies to hepatitis B core antigen (anti-HBc).

Background:

Hepatitis B virus (HBV) is a major human pathogen that causes acute and chronic hepatitis, cirrhosis and hepatocellular carcinoma (for a review, see Ganem and Prince, 2004). HBV is an enveloped virus with a partially duplex circular DNA genome of approximately 3,200 bases. Most primary infections in adults are self-limited, the virus is cleared from blood and liver, and individuals develop a lasting immunity. Less than 5 percent of infected adults develop persistent infections that can be asymptomatic (i.e. a carrier state). Twenty percent of chronically infected individuals can develop cirrhosis. Chronically infected subjects have 100 times higher risk of developing hepatocellular carcinoma than noncarriers. HBsAg becomes detectable in blood 30 to 60 days after infection followed by emergence of anti-HBc. Viremia develops by the time HBsAg is detected, and can reach 10^9 – 10^{10} virions/ml in acute infections. Upon clearance of the HBV infection by the immune response, the HBsAg antigen disappears from the circulation and anti-HBc usually remain indefinitely. In chronically infected individuals, HBsAg and anti-HBc usually remain for life, and lower viral titers can be detected in blood for a long period, but tend to decline over time.

The risk of transfusion-transmitted HBV infection was dramatically reduced after the development of HBsAg tests to screen blood donations in the late 1960s and 1970s. In the US, blood donors are screened for HBsAg and anti-HBc antibodies. Currently, HBV is transmitted by blood transfusions more frequently than HCV and HIV. The residual risk of posttransfusion HBV infection using the HBsAg and anti-HBc screening tests has been estimated as 1:63,000 (Schreiber et al., 1996) to 1:180,000 (Busch, December 2001, FDA Workshop) donations. The recent implementation of NAT to screen blood for HIV and HCV significantly reduced the risk for HCV and HIV infections from blood transfusions to $1:1.6 \times 10^6$ and $1:1.9 \times 10^6$ donations respectively (Busch, December 2001, FDA Workshop). Depending on the sensitivity of the test, implementation of HBV NAT has the potential to reduce the risk of posttransfusion HBV infection to levels similar to HIV and HCV.

Discussion:

During the serologically negative window period (WP), blood from infected individuals can transmit hepatitis B. Look-back studies using Polymerase Chain Reaction (PCR) showed that HBV DNA can be traced to the donor's blood. A recent European study of 3.6 million blood donations screened by HBV NAT using minipools of 96-samples (Roth et al., 2002) detected 6 PCR-positive serology-negative cases, but did not detect 37 out of 432 HBsAg-positive donations and an undetermined number of anti-HBc reactive donations (most Europeans do not use anti-HBc for screening blood donors). This study concluded that HBV minipool NAT in conjunction with anti-HBc would reduce the residual risk of transfusion-transmitted HBV. The US study conducted by Roche Molecular Systems in 581,790 volunteer whole blood donations screened by HBV NAT using minipools of 24-samples (a smaller minipools size than the European study) detected 2 WP cases, claims to have detected all *bonafide* HBsAg-positive donations (103 samples), and detected 12 out of 2,989 donations reactive only for anti-HBc. According to this study, the use of the COBAS AmpliScreen HBV test in conjunction with the anti-HBc antibody test would reduce the residual risk of transfusion-transmitted HBV and could be used as an alternative to the HBsAg donor screening test. However, the small number of discordant results in this study and the lack of follow up of 2 out of 4 HBsAg-positive only donations argues for caution, especially when considering the replacement of the HBsAg test, a highly reliable and sensitive blood screening test that has been used for more than 3 decades. Undoubtedly, implementation of more sensitive individual donation (ID) HBV NAT would further reduce the rate of transfusion-transmitted HBV (Allain, 2004; Busch, 2004; Biswas et al., 2003; Kleinman et al., 2003; Kuhns et al., in press). However, ID HBV NAT for donor screening is not currently available, and the infrastructure required to implement nationwide ID NAT will take several years to develop.

Roche Molecular Systems submitted a BLA for the COBAS AmpliScreen HBV test, which is a nucleic acid amplification test for the qualitative detection of HBV DNA in human plasma. The intended uses are:

- a) To screen plasma samples from donors of Whole Blood and blood components, Source Plasma and other living donors in conjunction with licensed anti-HBc tests.
- b) To screen specimens from living organ donors
- c) To replace licensed HBsAg tests with NAT for screening human plasma.

For donations of Whole Blood and blood components for transfusion, plasma will be tested in pools of not more than 24 individual donations. For Source Plasma, pools will comprise of not more than 96 donations. Please note that the 96-sample minipool NAT for Source Plasma donors will not be discussed in this Advisory Committee Meeting.

The objective of the study was to detect HBV infection in the WP. All blood is currently tested by both HBsAg and anti-HBc assays. Still, the major cause of HBV transmission by blood is from asymptomatic donors who have not yet developed HBsAg (i.e., WP) or chronic cases where serological markers are not detected (occult hepatitis B). Roche claims that their 24-sample minipool HBV NAT can detect HBV DNA in the HBsAg- and anti-HBc-negative WP of infection and in chronic cases. Roche also claims that additional HBV positive donations were identified using their modified NAT/anti-HBc testing algorithm than the current algorithm (HBsAg/anti-HBc). Thus, Roche seeks a claim to replace the HBsAg screening tests by 24-sample minipool NAT. Data will be presented with regard to these claims, and the Committee will be asked to advise FDA on scientific issues pertinent to establishing an appropriate role of HBV NAT in minipools for increasing the safety of the blood supply.

Questions for the Committee:

FDA would like the Committee to discuss the scientific merit and public health risk:benefit ratio for replacement of HBsAg testing by HBV NAT in a blood donor setting, and for use of HBV NAT in addition to continued donor screening for HBsAg. More specifically, the Committee will be asked the following questions:

1. Do the sensitivity and specificity of the Roche COBAS AmpliScreen HBV test in minipools of 24-samples support licensing of the assay as a donor screen?

If so,

2a. Assuming continued use of screening tests for anti-HBc, do the data support use of the Roche COBAS AmpliScreen HBV test in minipools of 24-samples to screen blood for transfusion as an equivalent alternative to the HBsAg test?

2.b. If the data do not support use of the Roche COBAS AmpliScreen HBV test in minipools of 24-samples as an equivalent alternative to HBsAg to screen blood for transfusion, what additional data would be required to validate such use?

3. Do the data support use of the Roche COBAS AmpliScreen HBV test on minipools of 24-samples to screen blood for transfusion as an added test in conjunction with licensed donor screening tests for HBsAg and anti-HBc?

References

- Allain J-P. Occult hepatitis B virus infection: implications in transfusion. *Vox Sang* 2004; 86:83-91.
- Biswas R, Tabor E, Hsia CC, Wright DJ, Laycock ME, Fiebig EW, Peddada L, Smith R, Schreiber GB, Epstein JS, Nemo GJ, Busch MP. Comparative sensitivity of HBV NATs and HBsAg assays for detection of acute HBV infection. *Transfusion* 2003; 43:788-798.
- Busch MP. Should HBV DNA NAT replace HBsAg and/or anti-HBc screening of blood donors? *Transfusion Clinique et Biologique* 2004; 11:26-32.
- Ganem D, Prince AM. Hepatitis B virus infection – Natural history and clinical consequences. *N. Engl. J. Med.* 2004; 350:1118-1129.
- Kleinman SH, Kuhns MC, Todd DS, Glynn SA, McNamara A, DiMarco A, Busch MP for REDS. Frequency of HBV DNA detection in US blood donors testing positive for the presence of anti-HBc: implications for transfusion transmission and donor screening. *Transfusion* 2003; 43:696-704.
- Kuhns MC, Kleinman SH, McNamara AL, Rawal B, Glynn S, Busch MP. Lack of correlation between HBsAg and HBV DNA levels in blood donors who test positive for HBsAg and anti-HBc: implications for future HBV screening policy. In press, 2004.
- Roth WK, Weber M, Petersen D, Drosten C, Buhr S, Sireis W, Weichert W, Hedges D, Seifried E. NAT for HBV and anti-HBc testing increase blood safety. *Transf.* 2002; 42:869-875.
- Schreiber GB, Busch MP, Kleinman SH, Korelitz JJ. The risk of transfusion-transmitted viral infections. *N. Engl J Med.* 1996; 334:1685-1690.

Anti-HBc - / HBsAg + / DNA -

Diagnostics

- Action
 - Test index donation by Alternate NAT
 - If Alternate NAT positive, quantitate
 - Enroll in follow-up study
- Four donors were in this category. Two donors completed follow-up study, two have follow-up results pending.

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Follow-up Study

Diagnostics

- Donor enrolled in the follow-up study were to return weekly for the first month and then monthly for 5 months for a total of 6 months
- Testing was to include the following:
 - IgM anti-HBc
 - anti-HBc (total)
 - anti-HBs
 - HBsAg
 - HBV DNA

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Follow-up Subject HA130002

Diagnostics

Day	Anti-HBc	HBsAg	HBV DNA	Anti-HBs	IgM Anti-HBc
Index	NR	Positiv	Negative	ND	ND
73	NR	NR	Negative	Negative	Negative
98	NR	NR	Negative	Negative	Negative
131	NR	NR	Negative	Negative	Negative
155	NR	NR	Negative	Negative	Negative

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Follow-up Subject DA120004



Diagnostics

Day	Anti-HBc	HBsAg	HBV DNA	Anti-HBs	IgM Anti-HBc
Index	NR	Positiv	Negative	ND	ND
69	NR	RR*	Negative	Positive	Negative
126	NR	RR*	Negative	Positive	Negative
154	NR	RR*	Negative	Positive	Negative
181	NR	RR*	Negative	Positive	Negative

* The HBsAg was repeat reactive but negative on neutralization.

Anti-HBc - / HBsAg - / DNA +



Diagnostics

- Action
 - Test index donation by Alternate NAT
 - If Alternate NAT positive, quantitate
 - Enroll in follow-up study
- Twenty-three donors were in this category.

Potential Window Cases



Diagnostics

- 23 Donors were HBV DNA + / HBsAg - / Anti-HBc -
 - 14 were enrolled into the follow-up study
 - 2 confirmed Window Period cases
- 12 presumed false positive due to persistently negative Anti-HBc, HBsAg and HBV DNA
 - 9 subject declined follow-up (calculated as false positive for sensitivity/specificity determination)

Blood Supply Safety: Other Data



Diagnostics

- Independent data comparing NAT testing for other blood-borne pathogens indicate HBV NAT testing likely to increase blood safety based upon comparative NAT precedent.
- Presumed "Window" cases detected indicate WNV > HBV > HCV > HIV

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Results of NAT Screening in the US From: M Busch EPFA (Paris May 2004)



Diagnostics

Stramer, Glynn, Kleinman, Caglioti, Strong, Busch. NEJM, in press
Gandhi, Strong, Kleinman et al. Blood102 (11):192A, 2003
Morb Mortal Wkly Rep 52:1160

Virus	Dates	Units Tested	NAT+/Ab-
HCV	4-10/99 to 12/04	53.3 million	230 (1/230,000)
HIV	4/89-12/00 to 12/04	50.3 million	18 (1/3.1 million)
HBV	8/02 to 12/04	1.7 million	5 (1/340,000)
WNV	7/03 to 11/04	4.8 million	968 (1/5,000)

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Conclusion



Diagnostics

- The COBAS AmpliScreen HBV Test is suitable for blood screening with a mini-pool strategy
- The COBAS AmpliScreen HBV Test has identified individuals in the pre-seroconversion window period.
- These data suggest that HBV MP-NAT should increase blood safety, and may provide an alternative to HBsAg screening.

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Acknowledgments

Diagnostics

- Clinical Trial Sites and Personnel
 - Gulf Coast Regional Blood Center
 - Community Blood Center of Greater Kansas City
 - Memorial Blood Center
 - BloodSource
 - Puget Sound Blood Center
- Larry Pietrelli, MA & Roche Molecular Clinical Affairs

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Back-up Slides

Diagnostics

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Pool Reactivity (Pools of 24)

Diagnostics

Category	Number of Pools	Percentage
Pools Tested	25,645	100%
Non-Reactive Pools	25,695	99.42%
Initially Reactive Pools	150	0.58%
Initial pools with Positive COBAS resolution and concordant serology	85	0.33%
Positive pools due to window cases	2	0.008%
Initially reactive pools with negative COBAS resolution	51	0.2%
Initial pools with positive COBAS resolution and without concordant serology	9	0.03%
Initial pools with 2 positive COBAS resolution: one concordant one not	3	0.01%

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Anti-HBc + / HBsAg + / DNA -

Diagnostics

- 16 Specimens met this criterion
- All specimens to be tested by Individual Nucleic Acid Testing (INAT)
- All specimens to be tested by Alternate NAT
- If Alternate NAT positive, the specimen was quantitated using the Alternate NAT Assay
- Donors were not enrolled into follow-up

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Anti-HBc + / HBsAg + / DNA -

Diagnostics

ID NAT		Alternate NAT		Quantitation (copies/mL)
Positive	10	Positive	7	200
		Negative	2	NA
		Not Done	1	NA
Negative	5	Positive	2	<100
		Negative	2	NA
		Not Done	1	NA

ID NAT and Alternate NAT not performed on one specimen

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Follow-up Study

Diagnostics

- Donors enrolled in the follow-up study were to return weekly for the first month and then monthly for 5 months for a total of 6 months
- Testing included the following:
 - IgM anti-HBc
 - anti-HBc (total)
 - anti-HBs
 - HBsAg
 - HBV DNA

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HBV DNA Positive Specimens

Diagnostics

- 11 Specimens were positive for HBV DNA by ID NAT
 - 8 Specimen tested by Alternate NAT (NGI)
 - 2 positive (1100 and 1200 copies/mL)
 - 6 negative (4 of the 6 were positive for either anti-HBs or IgM anti-HBc)
- 6 Donors were enrolled into the follow-up study
 - All 6 gave consistently negative ID NAT results during follow up

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Follow-up Subject HA130001

Diagnostics

Date	Anti - HBc	HBsAg	HBV DNA	Anti- HBs	IgM Anti-HBc
Index	RR	NR	Positive *	RR	NR
28	RR	NR	Negative	RR	NR
56	RR	NR	Negative	RR	NR
182	RR	NR	Negative	RR	NR

* = 1200 copies/mL

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Follow-up Subject AA110007

Diagnostics

Date	Anti - HBc	HBsAg	HBV DNA	Anti- HBs	IgM Anti-HBc
Index	RR	NR	Positive *	RR	NR
18	RR	NR	Negative	RR	NR
24	NR	NR	Negative	RR	NR
32	RR	NR	Negative	RR	NR

* = NOT negative

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Follow-up Subject HA130003



Diagnostics

Date	Anti - HBc	HBsAg	HBV DNA	Anti- HBs	IgM Anti-HBc
Index	RR	NR	Positive *	ND	ND
86	NR	NR	Negative	NR	NR
139	NR	NR	Negative	NR	NR

* - NOT Negative

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Anti-HBs Test Results



Diagnostics

Result	Ortho N = 303		Abbott N = 450	
	Positive	Negative	Positive	Negative
Total (%)	200 (66.0%)	103	232 (51.5%)	218

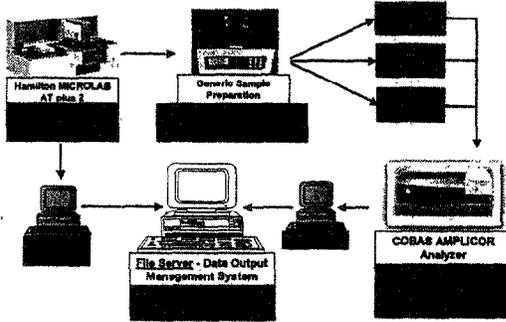
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**Non-clinical Performance Characteristics
of the COBAS AmpliScreen™ HBV Test -
An Assay for Blood Screening**

**Steven Herman, Ph.D.
Director, Blood Screening Development
Roche Molecular Systems, Inc.**

Diagnostics

COBAS AmpliScreen Assay System



Diagnostics

**Specimen Processing
Multiprep (mini-pools) and Standard (single
specimens)**

Multiprep Specimen Processing Mini-pools	Standard Specimen Processing Individual samples
Add 1,000 µL pool to screw cap tube	Add 200 µL specimen to screw cap tube
Centrifuge: 25,500 x g, 60 minutes, 2-4°C	Not done
Aspirate and discard 500 µL of supernatant	Not done
Add 600 µL Working Lysis Reagent	Add 600 µL Working Lysis Reagent
Incubate 10-15 minutes at room temperature	Incubate 10-15 minutes at room temperature
Add 700 µL Isopropanol	Add 800 µL Isopropanol
Centrifuge: 14,250 x g, 15-20 minutes, room temperature	Centrifuge: 14,250 x g, 15-20 minutes, room temperature
Aspirate and discard supernatant	Aspirate and discard supernatant
Add 1.0 mL 70% Ethanol	Add 1.0 mL 70% Ethanol
Centrifuge: 14,250 x g, 5-10 minutes, room temperature	Centrifuge: 14,250 x g, 5-10 minutes, room temperature
Aspirate and discard supernatant	Aspirate and discard supernatant
Resuspend pellet in 200 µL Multiprep Specimen Diluent	Resuspend pellet in 200 µL Multiprep Specimen Diluent
Use 50 µL for AmpliScreen HBV Test	Use 50 µL for AmpliScreen HBV Test

Diagnostics

Performance of "NAT + Anti-HBc" on HBsAg Positive Specimens

Diagnostics

	Total HBsAg Pos. Specimens: 918					
	NAT Alone			NAT + Anti-HBc		
	Pos	Neg	Sensitivity	Pos	Neg	Sensitivity
MP Test (1:24)	871	47	94.9%	917 [§]	0	100.0%
Std Test (neat)	898	20	97.8%	918	0	100.0%

* Positive by either or both NAT and anti-HBc
 § One specimen was NAT positive with Standard sample preparation (neat) and NAT negative with Multiprep (1:24). It was excluded from MP "NAT + anti-HBc" sensitivity calculation due to insufficient volume for anti-HBc test.

COBAS AmpliScreen HBV Test Non-clinical Performance Summary (1)

Diagnostics

- Analytical Sensitivity:
 - WHO Standard
 - Multiprep: ≥ 95% at 5 IU/mL
 - Standard: ≥ 95% at 15 IU/mL
 - CBER Panel
 - Multiprep: 100% (6/6) at 10 copies/mL
 - Standard: 92% (11/12) at 50 copies/mL
 - Clinical Specimens
 - Detected HBV DNA at higher dilution than HBsAg

COBAS AmpliScreen HBV Test Non-clinical Performance Summary (2)

Diagnostics

- Genotype inclusivity
 - Detected HBV Genotypes A-H
- Seroconversion panels
 - Detected HBV earlier than Ortho HBsAg Test System 3
 - Multiprep (1:24): average 17 days earlier than HBsAg
 - Standard (neat): average 22 days earlier than HBsAg
- Analytical Specificity and Potential Interfering Substances
 - No cross-reactivity or interference observed
- Clinical sensitivity in combination with anti-HBc assays
 - NAT + anti-HBc detected all confirmed HBsAg positive clinical specimens

Diagnostics

Thank you

**Data collected from the United States
IND Clinical Trials will be presented
next by Dr. Allan Frank**

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Diagnostics

Back-up Slides

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Diagnostics

Seroconversion Panel Tests
Detection of HBV DNA Prior to Abbott PRISM
HBsAg Test™

Seroconversion Panels

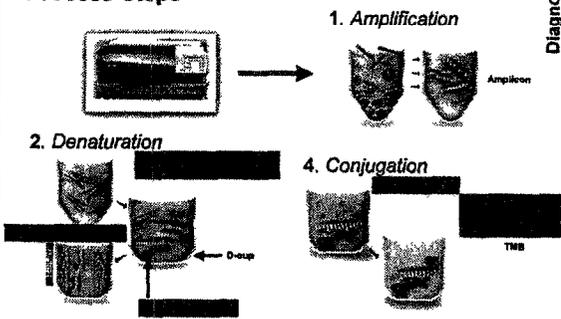
- Average number of days HBV DNA detected before HBsAg:
 - 14 days with Multiprep (1:24) and 19 days with Standard Preparation (neat)
- There were no panels in which HBsAg was detected prior to NAT
- The FEI licensed Abbott PRISM HBsAg Test (210a/95) was used

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COBAS AMPLICOR Analyzer
Process Steps



Diagnostics





Hepatitis B Virus Nucleic Acid testing (NAT) for Donors of Whole Blood

July 23, 2004 BPAC Meeting

Study Objectives

To determine whether the COBAS AmpliScreen HBV Test in minipools of 24-samples of plasma from volunteer blood donors can detect HBV DNA in

- ◆ HBsAg/anti-HBc negative window period cases (Primary Objective)
- ◆ HBsAg-positive donors (acutely infected and chronic carriers) and in persons previously exposed to HBV (Secondary Objective)



AGENDA

- ◆ Introduction and Background
Gerardo Kaplan, Chief LHREA, DETTD, FDA
- ◆ Serological Course of Hepatitis B
Jay H. Hoofnagle Director, Liver Disease Research Branch, Division of Digestive Diseases and Nutrition, NIDDK
- ◆ Preclinical and Clinical data of HBV Minipool (MP) NAT
Roche Molecular Systems
- ◆ FDA Perspective on HBV MP NAT and Questions for the Committee
Gerardo Kaplan



Clinical Trial in support of the application

- ◆ Identified 2 window period cases in 581,790 volunteer whole blood donations screened by HBV NAT using minipools of 24-samples
- ◆ RMS claims that the use of the COBAS AmpliScreen HBV test in conjunction with the anti-HBc test would reduce the residual risk of transfusion-transmitted HBV
- ◆ RMS claims that the COBAS AmpliScreen HBV test could be used as an alternative to the HBsAg donor screening test



ISSUE

FDA seeks the opinion of the Committee on the performance of the Roche COBAS AmpliScreen HBV test in minipools of 24-samples to screen blood for transfusion by nucleic acid testing (NAT), and its proposed intended use as an alternative to hepatitis B surface antigen (HBsAg) testing in conjunction with testing for antibodies to hepatitis B core antigen (anti-HBc).



Questions for the Committee

1. Do the sensitivity and specificity of the Roche COBAS AmpliScreen HBV test in minipools of 24-samples support licensing of the assay as a donor screen?



Questions for the Committee

If so,

- 2a. Assuming continued use of screening tests for anti-HBc, do the data support use of the Roche COBAS AmpliScreen HBV test in minipools of 24-samples to screen blood for transfusion as an equivalent alternative to the HBsAg test?
- 2.b If the data do not support use of the Roche COBAS AmpliScreen HBV testing minipools of 24-samples as an equivalent alternative to HBsAg to screen blood for transfusion, what additional data would be required to validate such use?



Questions for the Committee

3. Do the data support use of the Roche COBAS AmpliScreen HBV test on minipools of 24-samples to screen blood for transfusion as an added test in conjunction with licensed donor screening tests for HBsAg and anti-HBc?



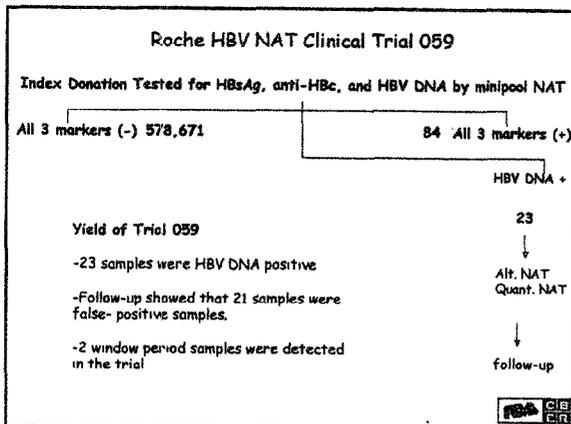
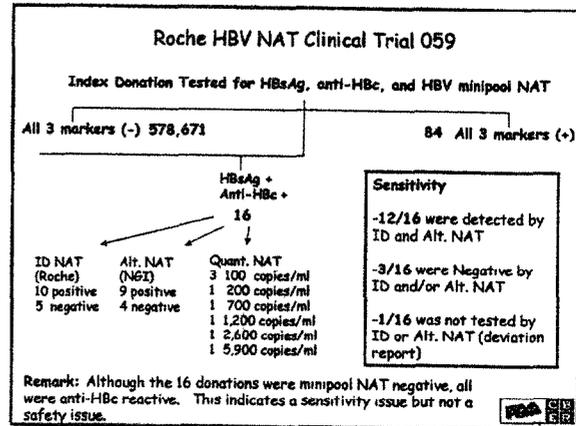
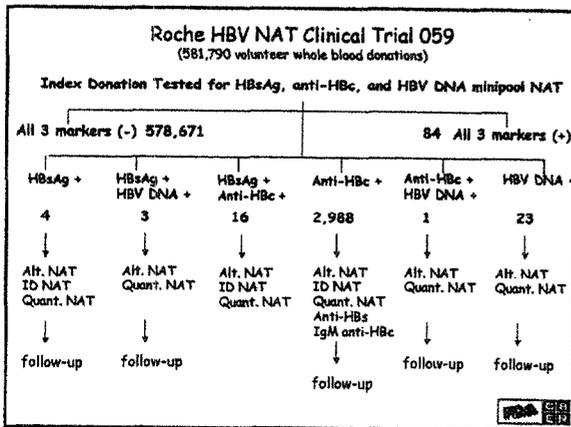
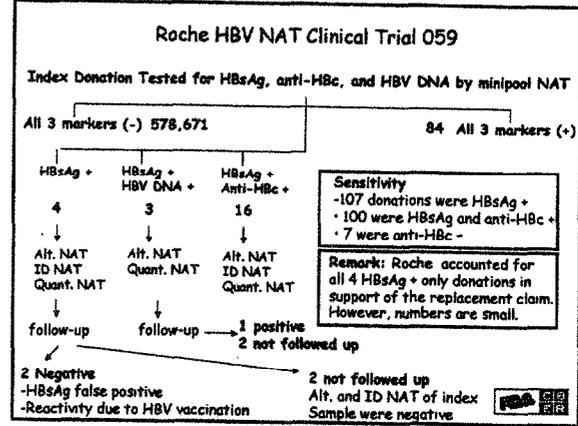


Hepatitis B Virus Nucleic Acid testing (NAT) for Donors of Whole Blood

FDA Perspective and Questions

Gerardo Kaplan, Ph.D., Chief, Laboratory of Hepatitis and Related Emerging Agents, DETTD, OBRR, CBER

July 23, 2004 BPAC Meeting



Questions for the Committee

1. Do the sensitivity and specificity of the Roche COBAS AmpliScreen HBV test in minipools of 24-samples support licensing of the assay as a donor screen?

Questions for the Committee

If so,

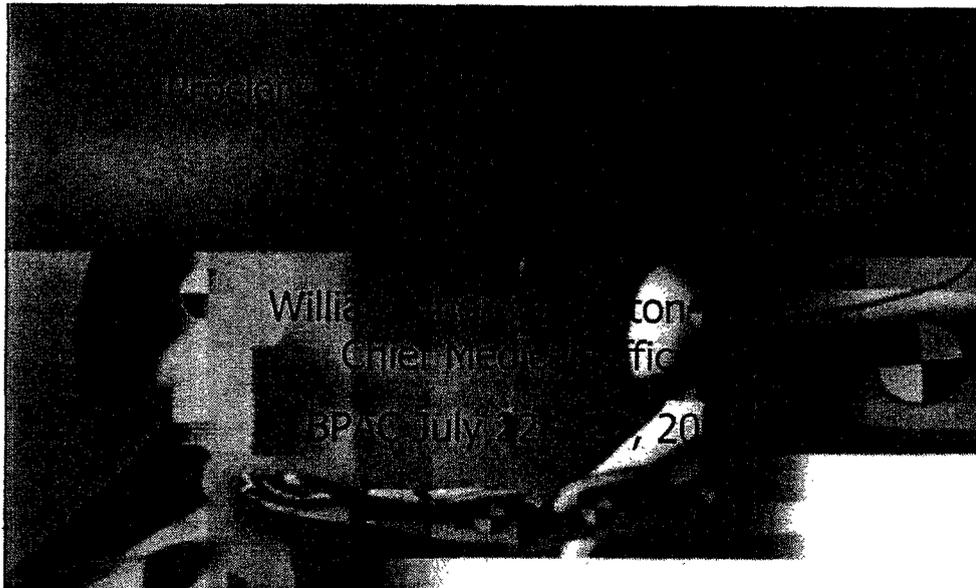
- 2a. Assuming continued use of screening tests for anti-HBc, do the data support use of the Roche COBAS AmpliScreen HBV test in minipools of 24-samples to screen blood for transfusion as an equivalent alternative to the HBsAg test?
- 2b. If the data do not support use of the Roche COBAS AmpliScreen HBV testing minipools of 24-samples as an equivalent alternative to HBsAg to screen blood for transfusion, what additional data would be required to validate such use?



Questions for the Committee

3. Do the data support use of the Roche COBAS AmpliScreen HBV test on minipools of 24-samples to screen blood for transfusion as an added test in conjunction with licensed donor screening tests for HBsAg and anti-HBc?





Procleix® Ultrio™ Assay

William J. Sullivan, M.D., M.Sc.
Chief Medical Officer
BPAC JULY 22, 2004

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 GEN-PROBE
Therapeutic Agents for HIV/AIDS
Procleix® Ultrio™ Assay

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Procleix® Ultrio™ Assay: Implementation issues

- ❖ CE Approval on 13 Jan 2004
- ❖ Worldwide Implementation
- ❖ Early yield cases
- ❖ Observed and modeled risk
- ❖ Current issues

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Available in the U.S. under FDA approved IND protocols.

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Post Tx HBV residual risk associated with testing/not testing for HBCoreAb

Routine Screening	Countries	Estimated Residual Risk
HBsAg + HBe	France, US	France* - 1: 640,000
		U.S. - 1: 301,000
HBsAg only	Rest of the World	Modeled @1: 40,000, assuming 0.5% HBCoreAb+ donors are viremic and 0.5% total donations are HBCoreAb+
		Italy - 1: 9,700
		Spain -1: 11,000
* Modeled on Incidence/window period		

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Implications of Multiplex HBV Testing

- **Blood Bank implementation issues include:**
 - Need for Tissue and Organ Donor testing claims
 - Need for false HBCoreAb+ donor re-entry
 - Use of NAT for resolving HBCoreAb true vs. false positives
- **Worldwide Issues have included:**
 - Higher than expected yield (often HBCoreAb+)
 - Analysis of HBV DNA+ rate in high HBCoreAb+ donor populations
 - Implications of vaccination on HBsAb+ to HBCoreAb seroconversions
 - Implications of vaccine escape mutants on HBV test results
 - Testing pool size relative to desired sensitivity

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**Statement of
The American Association of Blood Banks
Before the Blood Products Advisory Committee**

July 23, 2004

HBV NAT

**Presented by Harvey Alter, MD
Chief, Infectious Diseases Section
National Institutes of Health**

AABB is an international association dedicated to advancing transfusion and cellular therapies worldwide. Our members include more than 1,800 hospital and community blood centers and transfusion and transplantation services as well as approximately 8,000 individuals involved in activities related to transfusion, cellular therapies and transplantation medicine. For over 50 years, AABB has established voluntary standards for, and accredited institutions involved in, these activities. AABB is focused on improving health through the advancement of science and the practice of transfusion medicine and related biological therapies, developing and delivering programs and services to optimize patient and donor care and safety.

HBV remains the most common clinically important viral infection recognized after transfusion since the control of HIV and HCV infections through improved donor selection and serological and NAT screening. The data presented by Roche Molecular Systems from its IND study of HBV NAT in minipools of 24 samples are an important contribution to the ongoing improvement of donor testing.

AABB sees three issues of primary importance to the blood community to be addressed by BPAC and the Food and Drug Administration (FDA). First, is the Roche HBV assay approvable as a donor-screening test, and second, if approvable, shall its implementation be required in blood collection facilities? A third question is whether a claim for HBV NAT in minipools to replace HBsAg testing should be granted.

Regarding the first question, the data that are available for review by the AABB's Transfusion Transmitted Diseases Committee indicate that the Roche minipool HBV NAT assay appears to perform adequately in terms of analytical sensitivity and specificity, and generates incremental yield of NAT positive specimens over current serological tests. This suggests that the assay may be approvable in the currently proposed minipool NAT context, but its efficacy should be greater if it were applied to individual donations or significantly smaller minipools.

The second question is more difficult to answer. The minipool-based assay under consideration appears to yield between 1/250,000-300,000 positive donations that are negative on currently licensed tests for HBsAg and anti-HBcore. This rate is similar to the yield rate for HCV minipool NAT, and substantially higher than that for HIV NAT. It is comparable to or slightly higher than predicted by Biswas et al in a comparative study of NAT and serologic assays (Transfusion 2003;43:788-98).

As suggested from data on the evolution of markers of HBV infection, these donations tend to contain low copy numbers of HBV genome, and incomplete data suggest that some HBsAg assays, either available or under development for evaluation by FDA, may be able to interdict some of these "yield" donations. These include HBsAg tests from Abbott, Ortho Clinical Diagnostics and Genetic Systems. It is critical for the accurate analysis of the true impact of HBV minipool NAT that samples from these current yield cases, and those identified in the future by HBV NAT assays, be tested not only by the currently licensed serologic tests, but also by the developmental tests that are likely to be licensed in the future. Studies of the infectivity of yield cases are also desirable, and particularly of units that have concurrent HBV DNA and anti-HBs in the absence of detectable HBsAg and anti-HBc (as seen on two of the yield cases in the Roche trial).

Thus, despite measurable yield, introduction of HBV minipool NAT will offer only a minuscule increment in transfusion safety compared to currently required tests for HBsAg and anti-HB core. The result of this low incremental yield, coupled with low rates of chronic infection and clinical disease after HBV transmission, renders the marginal cost-effectiveness of HBV NAT in minipools very poor (see Jackson et al. Transfusion 2003;43:721-29). This cost-effectiveness will decline further into the future as a larger and larger proportion of the population has vaccine-induced immunity to HBV infection.

Regarding the third question, current data are not robust enough to support elimination of either serologic marker. It is possible that HBV NAT will eventually allow discontinuation of HBsAg screening, but this will require a larger data set including parallel testing by HBV DNA (likely on individual donations rather than minipools), anti-HB core, and HBsAg, using maximally sensitive antigen assays.

In summary, minipool HBV NAT is an expensive new screening assay that offers little clinical benefit and that will not be offset by discontinuation of any current testing. More sensitive HBsAg tests are available now and more will become available in the foreseeable future. More specific anti-HB core tests will also become available. Based on these considerations, AABB does not support a requirement for the use of NAT in minipools for blood donor screening at this time; rather, if HBV DNA NAT is licensed, its use should be optional. The requirement for HBV NAT testing should be reconsidered when technology allows for individual unit testing.