Review of BPAC Discussion and FDA's current thinking on HBV Minipool NAT

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ISSUE

- The FDA is considering an application for the first nucleic acid test (NAT) to screen blood donors for infection with the hepatitis B virus (HBV). (Another NAT for HBV is at an earlier stage of development.)

- If the first application is approved, a decision will be needed whether to recommend this test as an adjunct to current HBV screening by tests for hepatitis B surface antigen (HBsAg) and the antibody to hepatitis B core antigen (anti-HBc).

Introduction

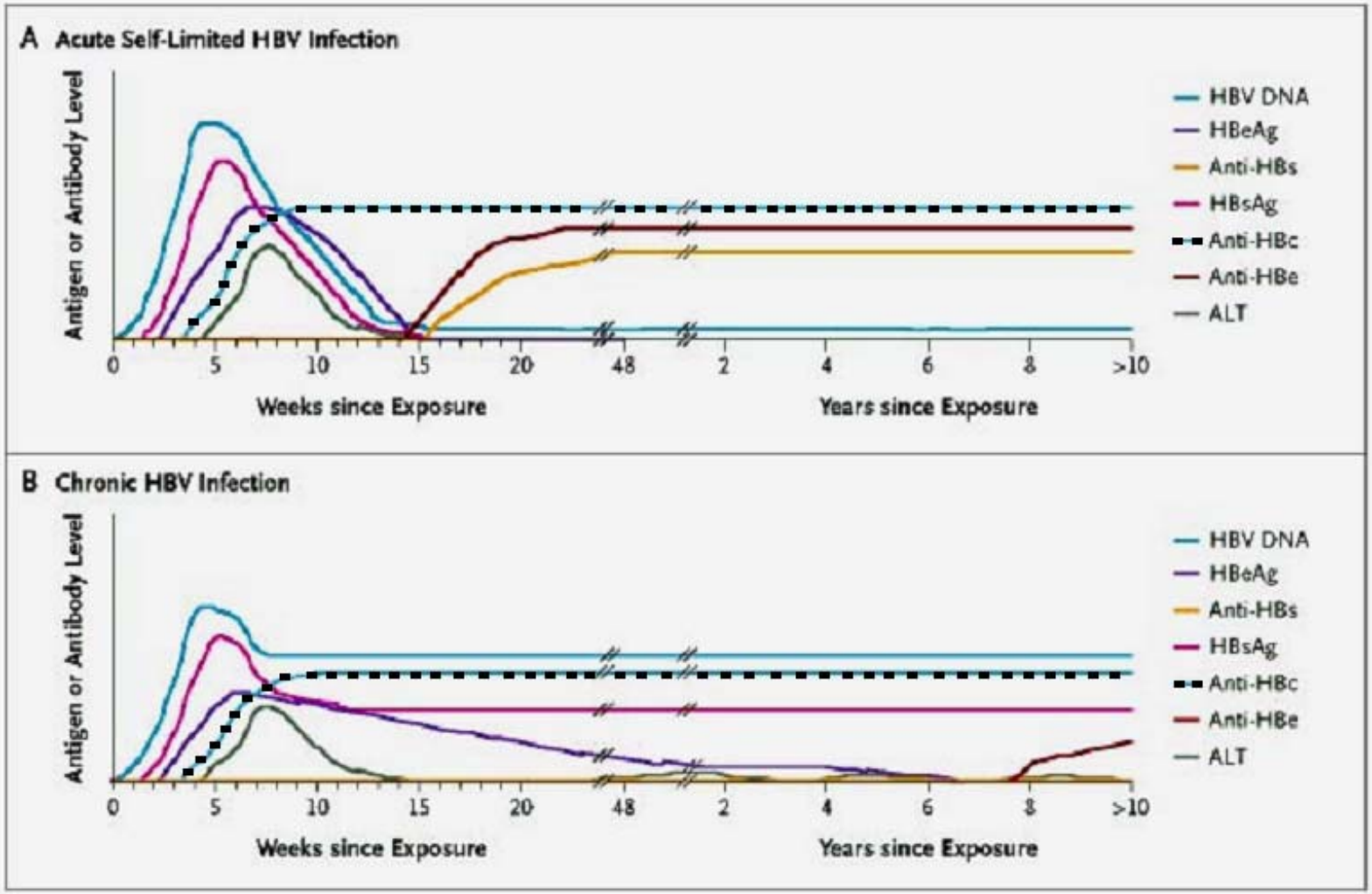
- Hepatitis B virus (HBV) is a major human pathogen that causes acute and chronic hepatitis in humans.

- Most primary infections in adults are self-limited, the virus is cleared from blood and liver, and individuals develop a lasting immunity.

Chronic Hepatitis B

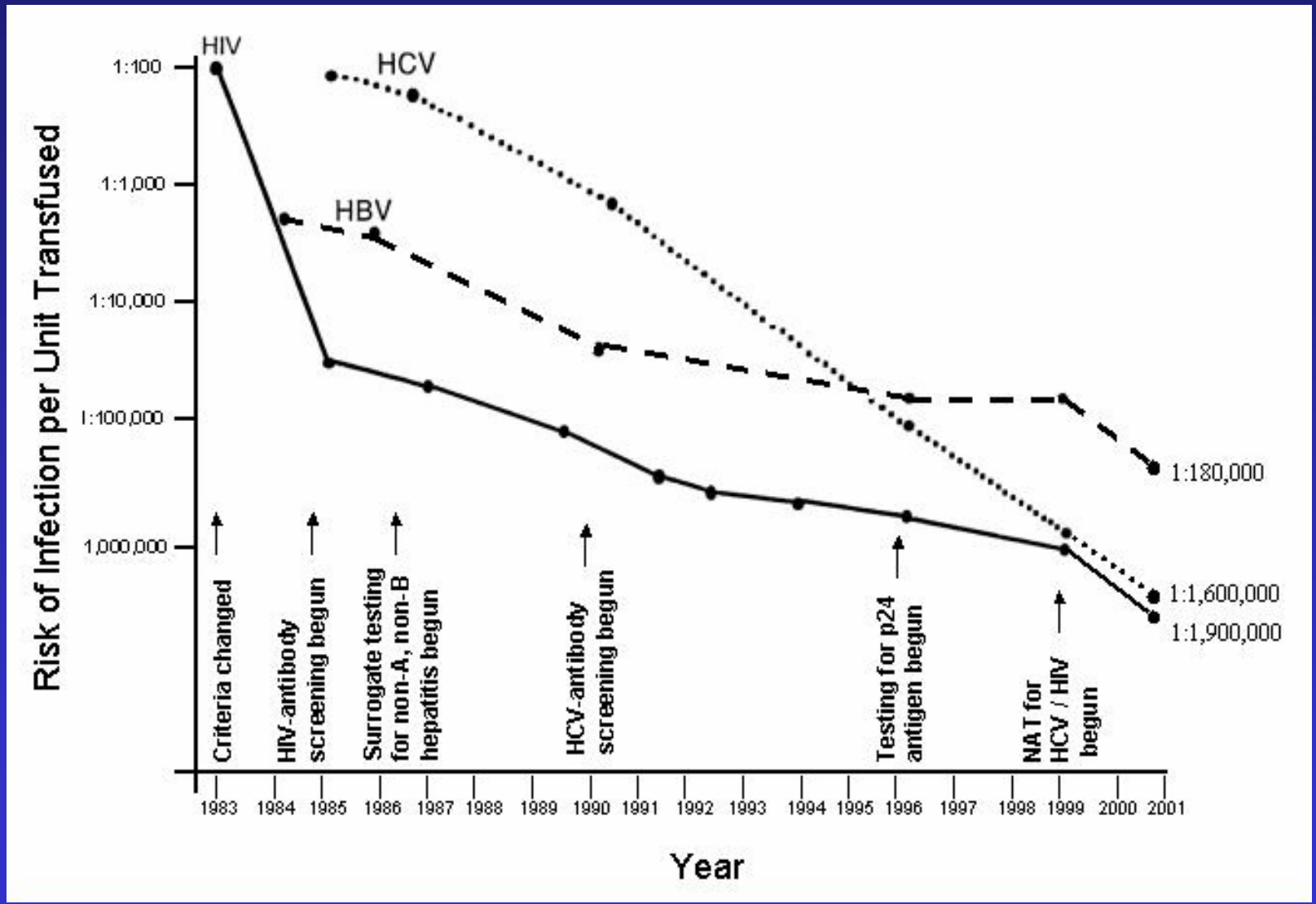
- Less than 5 percent of infected adults develop persistent infections that can be asymptomatic (i.e. a carrier state).
- Twenty percent of chronically infected individuals can develop cirrhosis.
- Chronically infected subjects have 100 times higher risk of developing hepatocellular carcinoma than noncarriers.

Serology of HBV Infection



Prince and Ganem, 2004. NEJM.

Risk of Viral Infections from Transfusion



Busch M., 2001. FDA Workshop.

Calculated Risk per Unit Transfused

	Serology Testing	Pooled NAT	Single Unit NAT
HIV	1:1,300,000	**1:1,900,000**	1:3,000,000
HCV	1:230,000	**1:1,600,000**	1:2,300,000
HBV	**1:180,000**	1:210,000	1:410,000

Data from FDA December 2001 Workshop: Presented by M. Busch, M.D. (Current risk estimates in **bold**)

Sources of Residual Risk

- Window period

  Time between exposure to an agent and detection with screening tests

- Viral variants (strains, subtypes) not detected by current tests
- Procedural testing errors

Roche COBAS AmpliScreen

HBV test in minipools

of 24-samples

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)
- All HBsAg-positive donors (Secondary Objective)

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

Roche HBV NAT Clinical Trial 059

(581,790 volunteer whole blood donations)

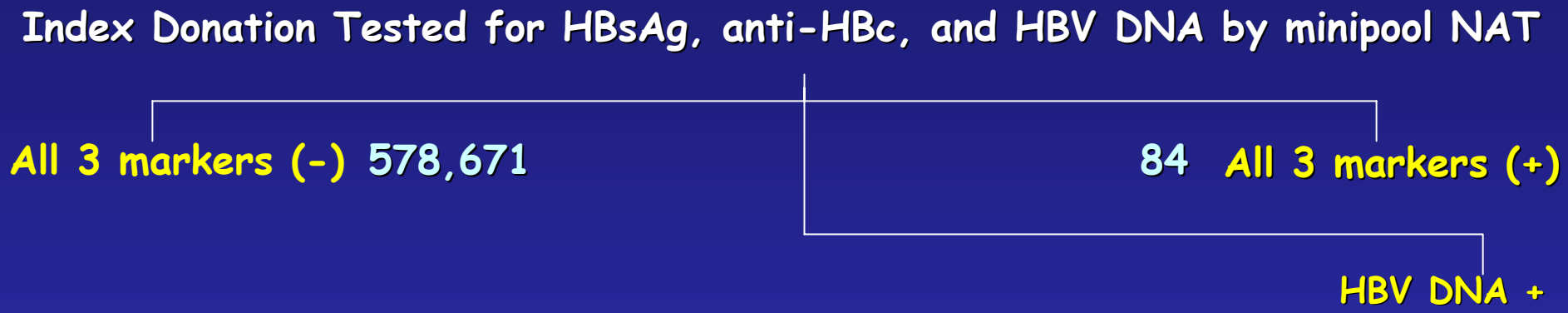
Index Donation Tested for HBsAg, anti-HBc, and HBV DNA minipool NAT

All 3 markers (-) 578,671

84 All 3 markers (+)

HBsAg +	HBsAg + HBV DNA +	HBsAg + Anti-HBc +	Anti-HBc +	Anti-HBc + HBV DNA +	HBV DNA +
4	3	16	2,988	1	23
Alt. NAT ID NAT Quant. NAT	Alt. NAT Quant. NAT	Alt. NAT ID NAT Quant. NAT	Alt. NAT ID NAT Quant. NAT Anti-HBs IgM anti-HBc	Alt. NAT Quant. NAT	Alt. NAT Quant. NAT
follow-up	follow-up		follow-up	follow-up	follow-up

Roche HBV NAT Clinical Trial 059



Yield of Trial 059

-23 samples were only HBV DNA positive

-Follow-up showed that 21 samples were false- positive samples.

-2 window period samples were detected in the trial

Alt. NAT
Quant. NAT

follow-up

Roche HBV NAT Clinical Trial 059

Index Donation Tested for HBsAg, anti-HBc, and HBV DNA by minipool NAT

All 3 markers (-) 578,671

84 All 3 markers (+)

HBsAg +	**HBsAg + HBV DNA +**	**HBsAg + Anti-HBc +**
4	**3**	**16**
↓	↓	↓
Alt. NAT ID NAT Quant. NAT	Alt. NAT Quant. NAT	Alt. NAT ID NAT Quant. NAT
↓	↓	
follow-up	follow-up →	**1 positive** **2 not followed up**

Sensitivity
-107 donations were HBsAg +
- 100 were HBsAg and anti-HBc +
- 7 were anti-HBc -

Remark: All 4 HBsAg + only donations resolved as FP in support of the replacement claim. However, numbers are small.

2 Negative
-HBsAg false positive
-Reactivity due to HBV vaccination

2 not followed up
Alt. and ID NAT of index Sample were negative

FDA CBER

Roche HBV NAT Clinical Trial 059

Index Donation Tested for HBsAg, anti-HBc, and HBV minipool NAT

All 3 markers (-) 578,671

84 All 3 markers (+)

HBsAg +
Anti-HBc +

16

ID NAT (Roche)
10 positive
5 negative

Alt. NAT (NGI)
9 positive
4 negative

Quant. NAT
3 100 copies/ml
1 200 copies/ml
1 700 copies/ml
1 1,200 copies/ml
1 2,600 copies/ml
1 5,900 copies/ml

Sensitivity

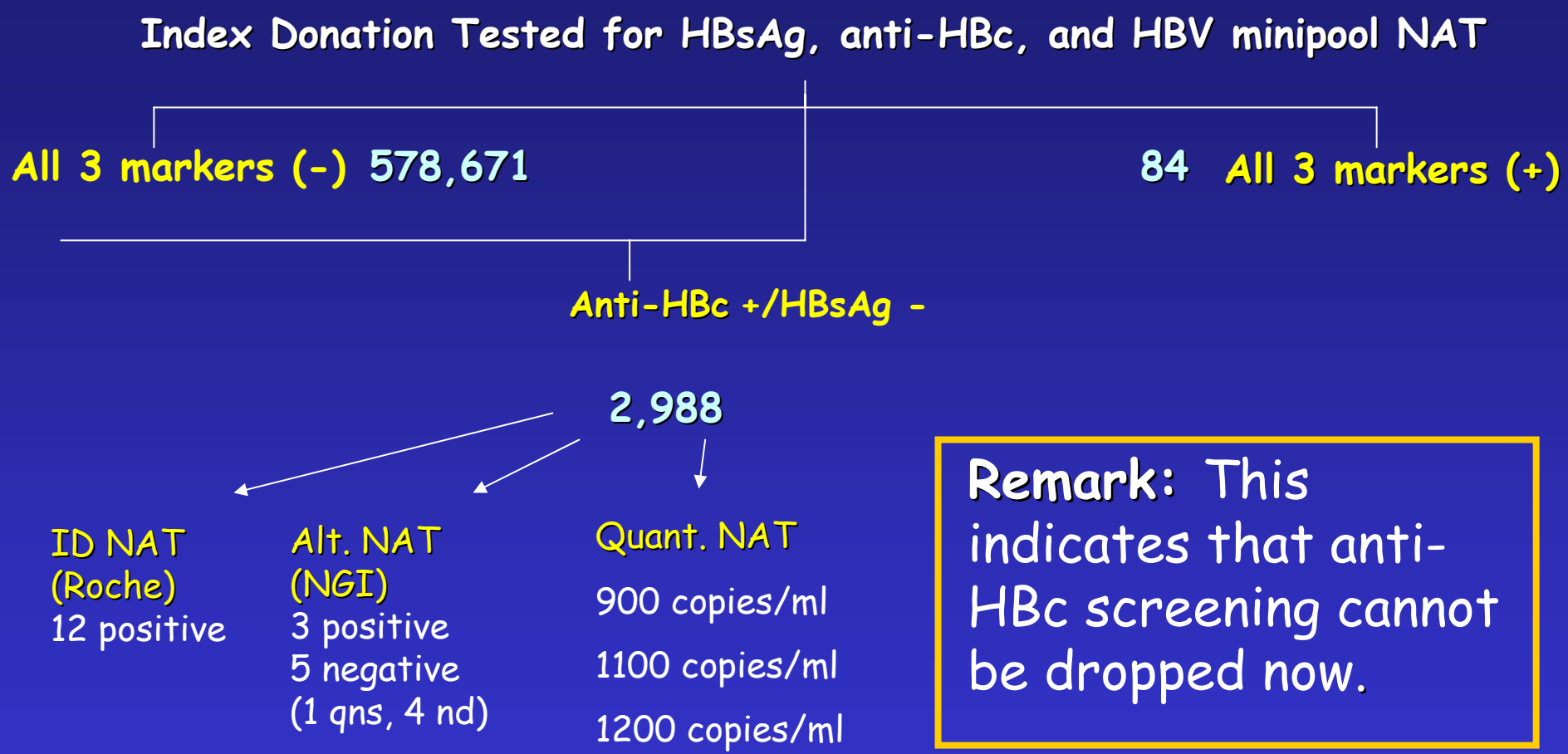
-12/16 were detected by ID and Alt. NAT

-3/16 were Negative by ID and/or Alt. NAT

-1/16 was not tested by ID or Alt. NAT (deviation report)

Remark: Although the 16 donations were minipool NAT negative, all were anti-HBc reactive. This indicates a sensitivity issue but not a safety issue, provided that screening for anti-HBc is retained.

Roche HBV NAT Clinical Trial 059



Remark: This indicates that anti-HBc screening cannot be dropped now.

On July 23, 2004, the Blood Products Advisory Committee (BPAC) analyzed the data in support of this application.

BPAC Questions & Answers

Q. 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?

A. 15, yes; 1, no; 0, abstentions. The nonvoting industry representative agreed with the "yes' vote.

BPAC Questions & Answers

If so,

Q. 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?

A. 16, no; 0, yes; 0, abstentions. The nonvoting industry representative agreed with the "no" vote.

BPAC Questions & Answers

Q. 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?

A. Committee members emphasized the need for additional data from clinical studies due to the small number of critical samples in Roche study. It was suggested that ID NAT would be a better replacement for HBsAg than MP NAT.

BPAC Questions & Answers

Q. 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?

A. The committee declined to vote on this question, but the individual members provided comments.

BPAC Questions & Answers

The following points emerged in comments:

- Whereas the test may identify some additional HBV positive donations, the public health benefits of routine additive testing are unclear.
- If a practical technology were developed, ID NAT for HBV would provide a greater benefit to blood safety than MP NAT.
- Useful studies of HBV NAT can be done in high risk groups as well as blood donors.

FDA's Policy Options

On the assumption that, in the near future, FDA is likely to approve the Roche COBAS AmpliScreen HBV test on minipools of 24 blood donor samples, the following policy options may need to be considered.

FDA's Policy Options

1. FDA could recommend the routine use of minipool HBV NAT to screen blood donors in conjunction with currently licensed serological tests for HBsAg and anti-HBc.

Pros & Cons

Pro: This option would add a third HBV test that may marginally increase the safety of the blood supply and thereby lower the residual risk of HBV from transfusion. FDA could provide an implementation date sufficiently far into the future to permit development of alternative HBV NAT tests compatible with non-Roche systems.

Pros & Cons

Con: An FDA recommendation for routine use of an additional test on blood donors would impose a significant added cost to the blood system, and increase the complexity of blood testing. Based on the implementation date for this recommendation, it might create logistic problems for the majority of blood collection centers that do not presently use the Roche assay system.

FDA's Policy Options

2. FDA could state that implementation of the Roche COBAS AmpliScreen HBV test is voluntary, but reserve the option for any future recommendation on routine use of HBV NAT on minipools of donor samples.

Pros & Cons

Pro: This option would allow blood centers to make local decisions regarding the value and practicality to test blood donations by HBV MP NAT.

Con: This option would most likely result in the implementation of minipool HBV NAT only in a number of blood collection establishments that currently use the Roche system for HIV and HCV NAT. This could create a public perception of two tiers of blood safety in the U.S.

FDA's Policy Options

3. FDA could regard all use of HBV NAT on minipools to be voluntary, but also encourage manufacturers to develop automated, high throughput systems to permit routine use of HBV NAT on individual donor samples

Pros & Cons

Pro: This option has the same benefits as Option 2, but creates an added expectation for development of a technology that FDA would be likely to recommend.

Con: As in option 2.

Conclusion

- As developed by Roche Molecular Systems, HBV NAT on pools of 24 samples can identify approximately 1:300,000 positive donations that fail detection by current screening tests for HBsAg and anti-HBc. (This is estimated to address only 25% of the current risk.)

- A global assessment of the public health benefits of donor screening for HBV by NAT on minipools would help FDA to make a policy decision whether to recommend such testing as an additive safety measure.