Potential Hepatitis B Virus (HBV) Device Reclassification

Maria Ines Garcia, PhD

Division of Microbiological Devices

Office of Health Technology 7: In Vitro Diagnostics

Office of Product Evaluation and Quality

Center for Devices and Radiological Health

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HBV Public Health Burden

- CDC estimates chronic HBV infection in US affects at least between 580,000 to 1.17 million people. (Ref 1)
- HBV infection can be asymptomatic→ HBV-infected individuals may be unaware of their HBV infection.
- Approximately 95% of adult patients with acute HBV infection (first 6 months after infection) recover completely, and 5% of adults develop chronic HBV. (Ref 2)
- Infants born to women who are hepatitis B surface antigen (HBsAg)-positive are at high risk of hepatitis B virus (HBV) infection. In absence of treatment, infants infected with HBV have a 90% risk of progression to chronic hepatitis B and up to 25% of infants who acquire chronic HBV infection will die prematurely from HBV-related hepatocellular carcinoma or cirrhosis. (Ref 2)

1. Centers for Disease Control and Prevention - Viral Hepatitis Q&As for Health Professionals (Available at https://www.cdc.gov/hepatitis/hbv/hbvfaq.htm#overview).
2. Centers for Disease Control and Prevention – Hepatitis B Surveillance Guidance (Available at https://www.cdc.gov/hepatitis/statistics/surveillanceguidance/HepatitisB.htm).

HBV Public Health Burden

- Patients with chronic HBV infection are at risk of developing liver damage, liver cancer, and liver failure.
- HBV can be reactivated in patients receiving immunosuppressive therapies, resulting in serious risk of liver failure or liver-associated death. (Ref 3)

→Diagnosis of patients for HBV infection with hepatitis B virus antibody and antigen tests is essential to ensure patients are linked to appropriate care.

3. Terrault, NA et, al., "Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance." Hepatology, 67(4): 1560-1599, 2018.

HBV Diagnosis (Ref 4)

- Adults: Screen all adults aged 18 years and older for HBV infection at least once during their lifetime (HBsAg, anti-HBs, and anti-HBc)
- Pregnant: Screen all pregnant people for HBsAg during each pregnancy

Test and Result	Interpretation	Action
HBsAg—Positive Total anti-HBc — Positive IgM anti-HBc — Positive Anti-HBs — Negative	Acute infection	Link to hepatitis B care
HBsAg — Positive Total anti-HBc — Positive IgM anti-HBc — Negative[1] Anti-HBs — Negative	Chronic Infection	Link to hepatitis B care
HBsAg — Negative Total anti-HBc — Positive Anti-HBs — Positive	Resolved Infection	Counsel about HBV infection reactivation risk
HBsAg — Negative Total anti-HBc — Negative[2] Anti-HBs — Positive	Immune from receipt of prior vaccination (if documented complete series)	If no documentation of full vaccination, then complete vaccine series per ACIP recommendations.
HBsAg — Negative Total anti-HBc — Positive Anti-HBs — Negative	Only core antibody is positive. See possible interpretations and corresponding actions.	
HBsAg — Negative Total anti-HBc — Negative[3] Anti-HBs — Negative	Susceptible, never infected (if no documentation of HepB vaccine series completion)	Offer HepB vaccine per ACIP recommendations

4. Centers for Disease Control and Prevention-Interpretation of Hepatitis B Serologic Test Results (Available at Screening and Testing Recommendations for Chronic Hepatitis B Virus Infection (HBV) | CDC

HBV Antigen Assays: Intended Use

Qualitative HBV Antigen Assays: The [HBV antigen assay name] is a [specify technology] for the qualitative detection of Hepatitis B surface antigen (HBsAg) in human adult and pediatric (2 years to 21 years of age) serum, serum separator tube, and plasma. The assay may also be used to screen for hepatitis B virus (HBV) infection in pregnant women to identify neonates who are at risk for acquiring hepatitis B during the perinatal period. Assay results, in conjunction with other laboratory results and clinical information, may be used to provide presumptive evidence of infection with HBV (state of infection or associated disease not determined) in persons with signs and symptoms of hepatitis and in persons at risk for hepatitis B infection.

HBV Antibody Assays: Intended Use

- **Qualitative Antibody Assays:** The [HBV antibody assay name] assay is an *in vitro* diagnostic immunoassay for use in the qualitative determination of total antibodies to the core antigen of the hepatitis B virus (HBV) in human adult serum and plasma. This assay can be used as an aid in the diagnosis of adults with acute or chronic hepatitis B virus (HBV) infection, and in the determination of the clinical status of HBV-infected individuals in conjunction with other HBV serological markers, for the laboratory diagnosis of HBV disease associated with HBV infection. This assay can also be used as an aid in the differential diagnosis in individuals displaying signs and symptoms of hepatitis.

- **Quantitative Anti-HBs Assays:** The [HBV Anti-HBV test name] assay is an *in vitro* quantitative determination of total antibodies to the hepatitis B surface antigen (HBsAg) in human adult, pregnant women, and pediatric (ages 2 to 21 years) serum and plasma (K_2EDTA and K_3EDTA). Assay results may be used as an aid in the determination of susceptibility to hepatitis B virus (HBV) infection for individuals prior to or following HBV vaccination; or where vaccination status is unknown. Assay results may be used with other HBV serological markers for the laboratory diagnosis of HBV disease associated with HBV infection. A reactive assay result will allow a differential diagnosis in individuals displaying signs and symptoms of hepatitis in whom etiology is unknown. The detection of anti-HBs is indicative of laboratory diagnosis of seroconversion from hepatitis B virus (HBV) infection or from vaccination.

HBV Antibody and Antigen Tests: Risks to Health

- **False Negative Results:**
  - Misdiagnosis of an infected patient/incorrect HBV infected status
    - Delay/failure to perform additional diagnostic procedures (e.g., assessing the severity of HBV-associated liver disease) and linkage to appropriate care.
    - Unnecessary testing in pursuit of another potential cause of hepatitis
    - Potential transmission of HBV to others
- **Minimize Potential Sources of False Negatives:**
  - Optimal sensitivity

HBV Antibody and Antigen Tests: Risks to Health

- **False Positive Results:**
- Misdiagnosis of an infected patient/incorrect HBV infected status
  - Unnecessary diagnostic procedures (e.g., HBV DNA)
  - Missed opportunity for vaccination
  - Psychological stress to the patient
- **Minimize Potential Sources of False Positives:**
  - Optimal Specificity

HBV Molecular Assay: Patient Management (Ref 4-6)

- Patient diagnosed with antibody and antigen assays → HBV DNA testing to guide treatment decisions.
- Current HBV treatments are life-long so patients receive regular HBV DNA testing.
  - Goal: sustained suppression of HBV replication
  - Result: improved serum ALT (liver enzymes), loss of HBeAg with or without detection of anti-HBe, and improvement in liver histology.

5. CDC Treatment https://www.cdc.gov/hepatitis/hbv/hbvfaq.htm #b15
6. Chronic Hepatitis B | AASLD: https://www.aasld.org/practice-guidelines/chronic-hepatitis b

HBV Molecular Assays: Intended Use

Quantitative HBV Molecular Assays: The [HBV DNA test name] assay is an *in vitro* polymerase chain reaction (PCR) assay to quantitate Hepatitis B Virus (HBV) DNA in human plasma or serum. The assay is intended for use as an aid in the management of patients with chronic HBV infection undergoing anti-viral therapy. The assay can be used to measure HBV DNA levels at baseline and during treatment to aid in assessing response to treatment. The results from the assay must be interpreted within the context of all relevant clinical and laboratory findings. This assay is not intended to be used for screening donors of blood, blood products, or cell, tissue, and cellular and tissue-based products (HCT/Ps) or as a diagnostic test to confirm the presence of HBV infection.

HBV Molecular Assays: Risks to Health

- **False Negative/Falsely Decreased Results, Incorrectly Interpreting the Test Results as a Negative Test Result or Failing to Correctly Operate the Test Causing a False Negative Test Result :**
  - Withholding, failure, or premature discontinuation of HBV antivirals
  - Potential transmission of HBV to others
  - Potential for other unnecessary medical procedures to investigate other causes of liver disease

- **Minimize Potential Sources of False Negatives, Incorrectly Operating Device Causing False Negatives, and Incorrectly Interpreting Results as Negatives:**
  - Optimal sensitivity

HBV Molecular Assays: Risks to Health

- **False Positive/Falsely Elevated Results, Incorrectly Interpreting the Test Results as a Negative Test Result, or Failing to Correctly Operate the Test Causing a False Negative Test Result:**
  - Administration or continuation of unnecessary antiviral treatment
  - Psychological stress to the patient
  - Unnecessary treatment
- **Minimize Potential Sources of False Positives, Incorrectly Operating Device Causing False Positives, and Incorrectly Interpreting Results as Positives:**
  - Optimal specificity

Additional Considerations

- Special Controls to mitigate risks (false positive/ false negative/ incorrect results/failure to correctly operate device)
- Goal: Maintain consistent high performance:
  - (1) Across devices with similar Intended Uses
  - (2) For individual devices over the Total Product Life Cycle (TPLC)

Questions for the Panel

1. Please comment on whether you believe FDA has identified a complete and accurate list of the risks to health presented by the following devices:

   (1) Qualitative HBV Antigen tests,
   (2) Qualitative HBV Antibody tests
   (3) Quantitative Anti-HBs tests, and/or
   (4) Quantitative HBV Molecular tests.

   Please comment on whether you disagree with inclusion of any of these risks or whether you believe any other risk should be included in the overall risk assessment of the devices listed above.

2. Please discuss potential mitigation measure(s)/control(s) that FDA should consider that could mitigate each of the identified risks
3. Based upon the information presented and future discussion at this panel meeting, please discuss whether, based on the available information, the Panel believes FDA should initiate the reclassification process for these devices from Class III to Class II, subject to special controls
4. Currently, there are no FDA authorized tests for the detection and quantitation of HBsAg. Please discuss the appropriate intended use for such a device, potential risks associated with the that intended use, and whether mitigation measure(s)/special control(s) could be developed that, in addition to general controls, to mitigate the risks to health.


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